AR

FR1574570

Patent number:	FR1574570
Publication date:	1969-07-11
Inventor:	
Applicant:	
Classification:	
- international:	A61K27/00
- european:	C07C51/60; C07C63/70; C07C65/21; C07C149/40; C07D207/32C5
Application number:	FRD1574570 19680725
Priority number(s):	US19670656074 19670726; US19680741348 19680701

Also published as:

- NL6810664 (A)
- GB1195628 (A)
- ES356485 (A)
- DE1770984 (A1)
- CH518929 (A5)
- BE718594 (A)
- SE338993 (B)
- NL162638C (C)

less <<

Report a data error here

Abstract not available for FR1574570

Data supplied from the ***esp@cenet*** database - Worldwide

RÉPUBLIQUE FRANÇAISE

MINISTÈRE DE L'INDUSTRIE

INSTITUT NATIONAL
DE LA PROPRIÉTÉ INDUSTRIELLE

(11) 1.574.570

BREVET D'INVENTION

(21) N° du procès verbal de dépôt ..... 160.668 - Paris.
(22) Date de dépôt ..... 25 juillet 1968, à 16 h 34 mn.
Date de l'arrêté de délivrance ..... 2 juin 1969.
(46) Date de publication de l'abrégé descriptif au *Bulletin Officiel de la Propriété Industrielle.* 11 juillet 1969 (n° 28).
(51) Classification internationale ..... **C 07 d.**

(54) **Procédé de production de composés de la classe des acides 5-benzoyl-pyrrole-alcanoïques.**

(72) Invention : John Robert Carson.

(71) Déposant : Société dite : McNEIL LABORATORIES, INCORPORATED, résidant aux États-Unis d'Amérique.

Mandataire : Cabinet Madeuf, Ingénieurs-Conseils.

(30) Priorité conventionnelle :

(32) (33) (31) *Brevets déposés aux États-Unis d'Amérique le 26 juillet 1967, n° 656.074 et le 1er juillet 1968, n° 741.348 au nom de John Robert Carson.*

1,195,628

PATENT SPECIFICATION

NO DRAWINGS

1,195,628

Date of Application (No. 35277/68) and filing Complete Specification: 24 July, 1968.

Application made in United States of America (No. 656,074) on 26 July, 1967.

Application made in United States of America (No. 741,348) on 1 July, 1968.

Complete Specification Published: 17 June, 1970.

Index at acceptance:—C2 C(1E1K3, 1E1K7, 1E7B1, 1E7B2, 1E7C1, 1E7C2, 1E7E1, 1E7F2, 1E7H1, 1E7H2, 1E7J, 1E7L, 1E7N5, 1E7P1, 1E7P3, 1K2A2, 1K2C2, 1Q2, 1Q4, 1Q6C, 1Q8A, 1Q9B, 1Q9D2, 1Q9E, 1Q11D, 1Q11G, 1Q11J, 2A3, 2A9, 2A11, 2R17, 2R19, 2T16, 3A8A4, 3A8B1, 3A8B2, 3A8C3, 3A8C4, 3A8D1, 3A8G1, 3A8G3, 3A8G4, 3A8J, 3A8K, 3A10E3D1, 3A10E5F1A, 3A10E5F2D, 3A10E5F3D, 3A19A4, 3A19B1, 3A19B2, 3A19B3, 3A19C2, 3A19C3, 3A19D2, 3C5A4, 3C5C2, 3C5C3, 3C5C7, 3C5E2, 215, 22Y, 220, 227, 25Y, 250, 251, 30Y, 305, 31Y, 313, 314, 32Y, 321, 326, 332, 338, 34Y, 342, 346, 351, 355, 36Y, 364, 365, 366, 367, 368, 574, 584, 62X, 621, 628, 631, 65X, 656, 658, 660, 661, 662, 665, 666, 675, 701, 719, 79Y, 790, 17X—195—282, KR, KS, LY, LZ, MB, MC, MD, MM, MV)

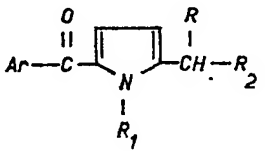
International Classification:—C 07 d 27/22, 27/26

COMPLETE SPECIFICATION

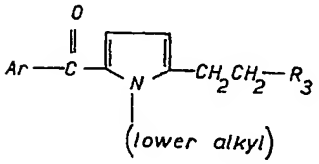
Aroyl-Substituted Pyrroles

We, McNEIL LABORATORIES, INCORPORATED, a Corporation organized and existing under the laws of the State of Pennsylvania, United States of America, of 110 Camp Hill Road, Fort Washington, State of Pennsylvania, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

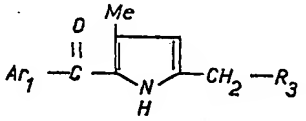
This invention relates to novel 5-aroylpyrroles, and, more particularly, to 5-benzoylpyrrole alkanoic acids and the corresponding salts, esters, nitriles, amides and substituted amides thereof. Said 5-aroyl-pyrroles may be represented by the following formulae:



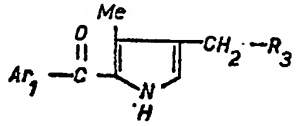
(I-a),



(I-b),



(I-c), or



(I-d),

wherein:

Ar represents a phenyl, monosubstituted phenyl or polysubstituted phenyl group, each substituent of said substituted phenyl group being a halogen atom, a lower alkyl, lower alkoxy, nitro, amino, cyano or methylthio group;

Ar_1 represents a phenyl, monosubstituted phenyl or polysubstituted phenyl group, each substituent of said substituted phenyl group being a halogen atom, a lower alkyl or lower alkoxy group;

R represents a hydrogen atom or a lower alkyl group;

R_1 represents a hydrogen atom, a lower alkyl or benzyl group;

R_2 represents a CN, COOH, COO-(lower alkyl), $CONH_2$, CONH-(lower alkyl) or CON-(lower alkyl)$_2$ group; and

SEE ERRATA SLIP ATTACHED

R_3 represents a COOH, COO-(lower alkyl), $CONH_2$, CONH-(lower alkyl) or CON-(lower alkyl)$_2$ group;

provided that:

(i) when Ar is a nitro-substituted phenyl or amino-substituted phenyl group, then R is a hydrogen atom, R_1 is a lower alkyl group and R_2 is a CN, COOH or COO-(lower alkyl) group;

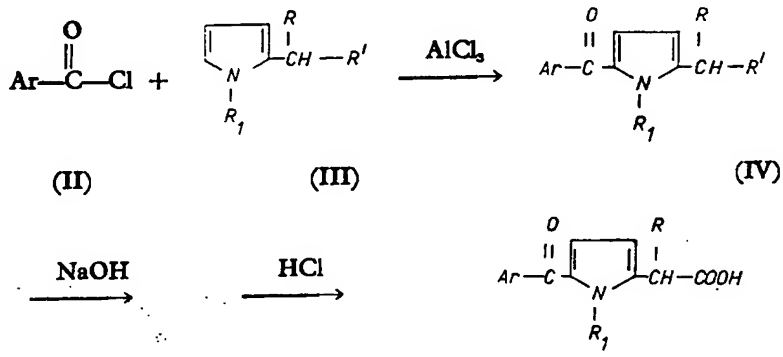
(ii) when Ar is a cyanophenyl or methylthiophenyl group, then R_1 is a lower alkyl group and R_2 is a COOH or COO-(lower alkyl) group; and

(iii) when R_1 is a hydrogen atom, then R is also a hydrogen atom.

The non-toxic, therapeutically acceptable salts of such acids, such as are obtained from appropriate organic or inorganic bases, are also embraced within the scope of this invention.

As used herein, " lower alkyl " and " lower alkoxy " may be straight or branch chained saturated hydrocarbons having from 1 to 6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl, and, respectively, the corresponding alkoxy groups such as methoxy, ethoxy, propoxy and isopropoxy.

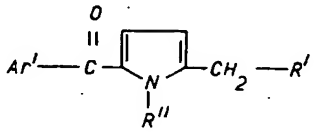
The compounds of the present invention may be obtained by means of several synthetic processes. For example, the compounds of formula (I—a), in which R_2 is CN or COO-(lower alkyl), are generally prepared by a Friedel-Crafts reaction between a benzoyl halide, preferably are chloride (II), and a pyrrole-2-acetic acid derivative of formula (III), wherein R' is a cyano or lower alkoxycarbonyl, in the presence of a Lewis acid, preferably a metalic halide such as aluminum chloride. Suitable solvents are those typically employed in a Friedel-Crafts reaction, such as methylene chloride, 1,2-dichloroethane, carbon disulfide or nitrobenzene. The acid derivative (IV) thus obtained can then be converted to the corresponding free carboxylic acid by conventional hydrolysis, for example, by heating a solution of (IV) in aqueous methanol with an alkali metal hydroxide to form the alkali metal salt of the acid and then acidifying the mixture. The foregoing reactions may be illustrated by the following schematic diagram.



(II) (III) (IV)

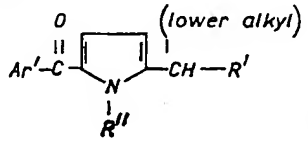
The benzoyl chlorides (II) are generally known and may be obtained by transformation of the corresponding benzoic acid to the acid chloride form according to conventional procedures, such as the procedure hereinafter demonstrated in Example LXXXI.

Alternatively, to prepare the nitriles, esters and acids of formula (I—a), wherein R is a lower alkyl, a 5-benzoyl-pyrrole-2-acetic acid derivative of the formula:



(V)

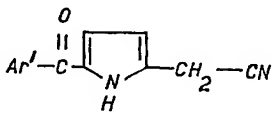
wherein R' is as previously described, R'' is lower alkyl or benzyl, and Ar' is phenyl or phenyl substituted with halogen, lower alkyl, lower alkoxy or cyano, which acid derivative (V) may be obtained in accordance with the aforementioned Friedel-Crafts procedure, is C-alkylated according to conventional alkylation techniques, e.g., with a lower alkyl halide as the alkylating agent in the presence of a strong base such as sodium amide or sodium hydride, to yield the corresponding nitriles and esters:



(VI)

from which the corresponding acids are obtained by conventional hydrolysis.

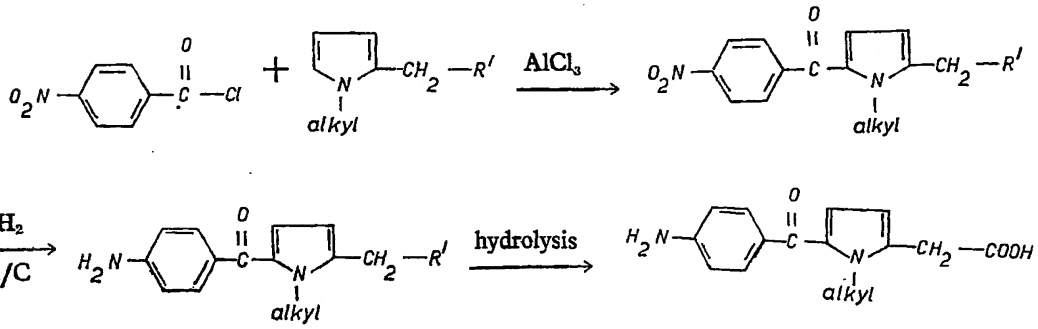
The acetonitriles of formula (VI), in which R'' is lower alkyl, are also obtained by conventional N-alkylation of an N-unsubstituted 5-benzoyl-pyrrole-2-acetonitrile of the formula:



(VII)

followed by conventional C-alkylation of the thus-obtained N - alkyl - 5 - benzoyl - pyrrole-2 - acetonitrile using an appropriate lower akyl halide as the alkylating agent in each step. After the N-alkylation step or the C-alkylation step, corresponding acids may be obtained by conventional hydrolysis.

The nitriles, esters and acids of formula (I—a), wherein Ar is an amino-substituted phenyl group, are preferably prepared from the corresponding 5 - nitrobenzoyl - 1 - (lower alkyl) - pyrrole - 2 - acetic acid esters or nitriles according to the following reaction scheme in which the corresponding *para*-derivatives are exemplified (R' being as previously described and the 'alkyl' being a straight or branched hydrocarbon having from 1 to 6 carbon atoms.)

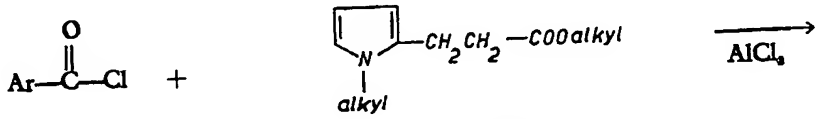


In the foregoing reaction sequence, the nitro function of the 5 - nitrobenzoyl - 1-(lower alkyl) - pyrrole - 2 - acetic acid ester or nitrile (obtained by the Friedel-Crafts type of reaction previously described) is catalytically hydrogenated, for example, with hydrogen and a palladium-on-carbon catalyst, to yield the corresponding 5 - aminobenzoyl - 1-(lower alkyl) - pyrrole - 2 - acetic acid ester or nitrile which is then hydrolyzed to the corresponding free acid form.

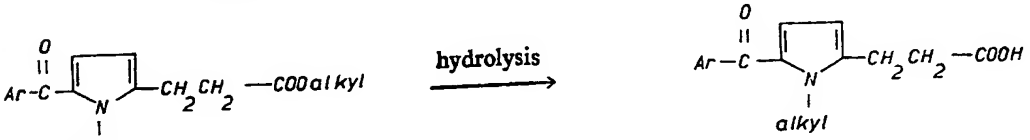
Esterification of the acids of formula (I—a) with a slight excess of an appropriate lower alkanol yields the corresponding esters, i.e., wherein R_2 equals COO-(lower alkyl). Preferably, the methyl esters of formula (I—a) are obtained by the Friedel-Crafts reaction previously described between an appropriate benzoyl halide (II) and an appropriate methyl pyrrole-2-acetate (III).

The primary amides of formula (I—a) are readily obtained by partial hydrolysis of the corresponding nitriles of formula (I—a). The nitrile-to-amide transformation is accomplished according to conventional procedures, for example, by treatment of the nitrile with aqueous sodium hydroxide under reflux for a relatively short time, that is, a period sufficient for partial hydrolysis to the amide stage as opposed to complete hydrolysis to the carboxylic acid stage. The corresponding lower alkyl-substituted amides are preferably obtained by first transforming the carboxylic function of the formula (I—a) acids into the corresponding acid chloride form, for example, by treatment of the acid or its alkali metal salt with thionyl chloride or oxalyl chloride, and then reacting the thus-obtained acid chloride with an appropriate lower alkylamine or di - (lower alkyl) - amine to yield the corresponding N-alkyl or N,N-dialkyl amides, respectively, of formula (I—a).

The compounds of formula (I—b), wherein R_3 is COO-(lower alkyl), preferably ethoxycarbonyl, and Ar is other than aminophenyl are prepared by a Friedel-Crafts reaction between an appropriate benzoyl halide, preferably the chloride (VIII), and a lower alkyl 1-(lower alkyl) - pyrrole - 2 - propionate (IX). Conventional hydrolysis of the thus-obtained lower alkyl 5 - benzoyl - 1 - (lower alkyl)-pyrrole - 2 - propionate (X) yields the corresponding free acids of formula (I—b). In turn, the acids may be converted to the corresponding amides of formula (I—b) according to conventional procedures using ammonia, or an appropriate alkyl or dialkyl amine.



(VIII) (IX)



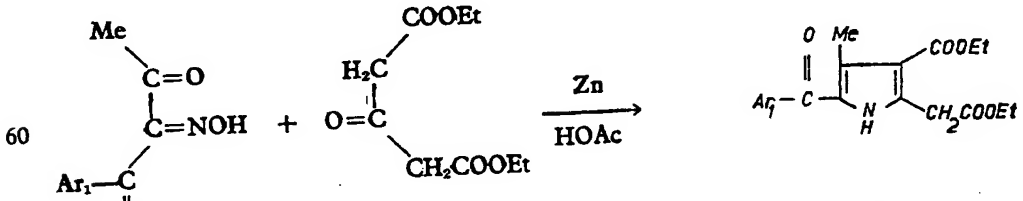
(X)

The 'alkyl' being a straight or branched hydrocarbon having from 1 to 6 carbon atoms.

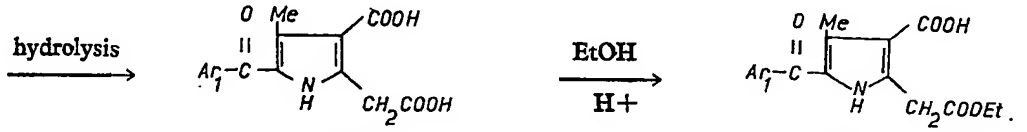
The formula (I—b) compounds, wherein Ar is aminophenyl, are preferably obtained from the corresponding lower alkyl 5 - nitrobenzoyl - 1 - (lower alkyl) - pyrrole - 2-propionate (obtained by the usual Friedel-Crafts type of reaction between nitrobenzoyl chloride and alkyl propionate IX) by transforming the nitro function to an amino function according to the reaction scheme previously described for the formula (I—a) compounds, i.e., by means of catalytic hydrogenation followed by hydrolysis.

The alkyl propionates (IX) may be prepared by first treating an appropriate N-alkylpyrrole - 2 - carboxaldehyde with an appropriate alkoxycarbonyl - methylene triphenylphosphorane [see R. Jones et al., Canad. Jour. Chem, *18*, 883 (1965)] and then hydrogenating the thus-obtained alkyl 2 - (1 - alkyl-2 - pyrrolyl) - acrylate, thereby saturating the double bond of the acrylate function, to yield the desired alkyl propionate (IX).

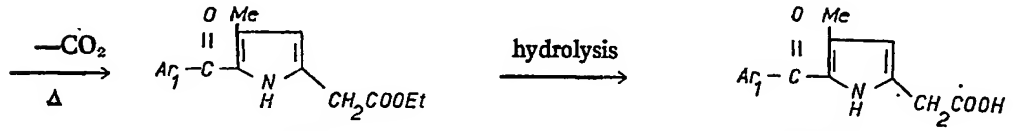
The compounds of formula (I—c) are prepared from an appropriate 1 - aryl - 1,2,3-butanetrione - 2 - oxime (XI) and an appropriate dialkyl acetonedicarboxylate (XII) as starting materials. The two are contacted together according to a Knorr pyrrole synthesis in glacial acetic acid in the presence of zinc dust to yield the ring-closed pyrrole, alkyl 5 - aroyl - 3 - alkoxycarbonyl - 4 - methyl-pyrrole - 2 - acetate (XIII). Hydrolysis of the latter with moderately concentrated alkali, for example 25—50% aqueous sodium hydroxide gives the corresponding free di-acid (XIV) which is then partially reesterified using an acidic solution of a lower alkanol to yield the corresponding alkyl 5 - aroyl - 3 - carboxy-4 - methylpyrrole - 2 - acetate (XV). Decarboxylation of the carboxy group in the 3-position is then accomplished by heating the latter in a suitable basic organic solvent such as quinoline. The resulting alkyl 5 - aroyl-4 - methylpyrrole - 2 - acetate (XVI) is then hydrolyzed in the usual manner to give the desired free acids (XVII) of formula (I—c). In turn, the acids may be esterified using lower alkanols to the corresponding lower alkyl esters of formula (I—c) or converted to the corresponding amides of formula (I—c) according to conventional procedures using ammonia, or an appropriate alkyl or dialkyl amine. The foregoing reaction sequence may be illustrated by the following diagrammatic scheme:



(XI) (XII) (XIII)

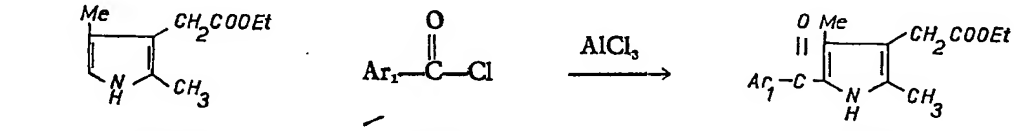


(XIV) (XV)

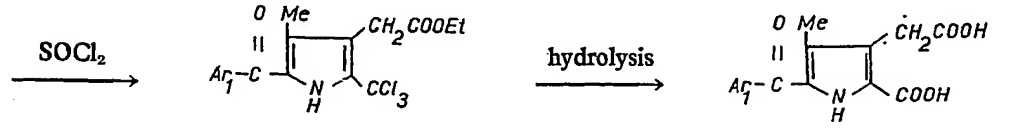


(XVI) (XVII)

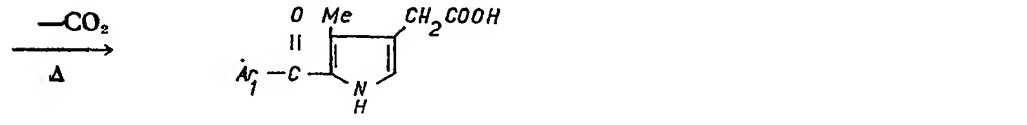
The compounds of formula (I—d) are prepared from the known pyrrole ester, ethyl 2,4 - dimethylpyrrole - 3 - acetate (XVIII), which is acylated according to a Friedel-Crafts reaction using an appropriate benzoyl halide, preferably the chloride (XIX), as the acylating agent. The methyl group in the 2-position of the thus-obtained ethyl 5 - benzoyl - 2,4-dimethylpyrrole - 3 - acetate (XX) is then perchlorinated by treating said ester (XX) with sulfuryl chloride in an inert solvent such as ether to yield the corresponding ethyl 5 - benzoyl - 4 - methyl - 2 - trichloromethylpyrrole - 2 - acetate (XXI). Hydrolysis of the last compound, for example, by heating at reflux in aqueous dioxane or 1,2 - dimethoxyethane, for a few hours, gives the di-acid, 5 - benzoyl - 4 - methyl - 2 - carboxy - pyrrole - 3 - acetic acid (XXII). The carboxy function on the 2-position is then removed, for example, by heating in a suitable basic organic solvent such as quinoline, to yield the desired free acids (XXIII) of formula (I—d). Again, the acids may in turn be converted to the corresponding esters and amides of formula (I—d) in the usual manner. The foregoing reaction sequence may be illustrated by the following diagrammatic scheme:



(XVIII) (XIX) (XX)



(XXI) (XXII)



(XXIII)

The corresponding salts of the acids of formulas (I—a, b, c and d) are readily obtained by treatment of the latter with an equivalent amount of appropriate base, for example, an alkali or alkaline earth metal hydroxide, e.g., sodium hydroxide, potassium hydroxide, barium hydroxide or calcium hydroxide, or with an organic amine base, e.g., a lower alkylamine such as ethylamine or propylamine, or other amines such as benzylamine, piperidine or pyrrolidine.

The compounds of formulas (I—a, b, c and d) and the therapeutically active salts thereof have useful pharmacological properties which make them suitable for incorporation into conventional pharmaceutical forms for administration. These compounds have been found to possess anti-inflammatory activity as demonstrated in the standard kaolin-induced rat paw edema and cotton pellet granuloma at doses ranging from 5—100 mg/kg body weight.

In the kaolin-induced rat paw edema assay, the ability of a compound, when administered in a single oral dose, to inhibit the swelling of the rat paw injected with a standard amount (0.1 ml.) of 10% kaolin suspension in saline is measured. For comparative purposes, the activity of the compound to be tested is measured against that produced by the known anti-inflammatory agent, phenylbutazine. Male Holtzman rats are used in the assay. For example, in this test, the compound 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole-2 - acetic acid was found to exhibit an inhibition of about 35% at 12.5 mg/kg; about 47% at 25 mg/kg; and about 45—53% inhibition in doses of 50—100 mg/kg; whereas phenylbutazone exhibited an inhibition of about 30—40% at 100 mg/kg.

In the cotton pellet granuloma assay, the ability of a compound, when administered orally to male Holtzman rats daily for seven days, to inhibit the amount of granuloma tissue formed in or around a cotton pellet implanted beneath the skin in the thoracic region of the animal is measured and compared to water controls. The method is described by Charles A. Winter and co-workers in J. Pharmacol., *141*, 369 (1963). Analysis of variance is used to determine the significance of the results. For example, in this test, the compound 5 (*p* - anisoyl) - 1 - methylpyrrole - 2 - acetic acid exhibited a granuloma weight of about 71 mg. at a dose of 25 mg/kg as compared to 110 mg. with the water controls; and the compound 5 - (*p*-chlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile exhibited a granuloma weight of about 98 mg. at a dose of 100 mg/kg as compared to 115 mg. with the water controls.

In the following table, the anti-inflammatory activities of several compounds of formulas (I—a, b, c and d) are listed, it being understood that such compounds are not listed for purposes of limiting the invention thereto, but only to exemplify the useful properties of all the compounds within the scope of formulas (I—a, b, c and d), including the pharmaceutically acceptable basic salts thereof.

TABLE I

Kaolin-Induced Paw Edema Assay

	Dose (p.o.) mg/kg	% Inhibition (Average 10 rats)
5-(*p*-chlorobenzoyl)-1-methylpyrrole-2-acetic acid	25	47
5-(*m*-chlorobenzoyl)-1-methylpyrrole-2-acetic acid	25	41
5-(*o*-chlorobenzoyl)-1-methylpyrrole-2-acetic acid	25	44
5-(2',4'-dichlorobenzoyl)-1-methylpyrrole-2-acetic acid	25	51
5-(*p*-bromobenzoyl)-1-methylpyrrole-2-acetic acid	25	42
5-(*p*-fluorobenzoyl)-1-methylpyrrole-2-acetic acid	25	42
5-(*p*-methoxybenzoyl)-1-methylpyrrole-2-acetic acid	25	42
5-(*p*-methylbenzoyl)-1-methylpyrrole-2-acetic acid	25	44
5-(*p*-nitrobenzoyl)-1-methylpyrrole-2-acetic acid	100	35
5-(*p*-aminobenzoyl)-1-methylpyrrole-2-acetic acid	25	23
5-(*p*-cyanobenzoyl)-1-methylpyrrole-2-acetic acid	100	20
5-benzoyl-1-methylpyrrole-2-acetic acid	25	38
5-(*p*-chlorobenzoyl)-1-methylpyrrole-2-(α-methyl)-acetic acid	50	56
5-(*p*-chlorobenzoyl)-1-methylpyrrole-2-(α-methyl)-acetic acid	25	22
5-(*p*-chlorobenzoyl)-pyrrole-2-acetic acid	25	32
5-(*p*-chlorobenzoyl)-1-ethylpyrrole-2-acetic acid	100	43
1-benzyl-5-(*p*-chlorobenzoyl)-pyrrole-2-acetic acid	50	23
ethyl 5-(*p*-chlorobenzoyl)-1-methylpyrrole-2-acetate	25	37
methyl 5-(*p*-chlorobenzoyl)-1-methylpyrrole-2-acetate	25	38
5-(*p*-chlorobenzoyl)-1-methylpyrrole-2-acetamide	50	35
5-(*p*-chlorobenzoyl)-1-methylpyrrole-2-(N-ethyl)-acetamide	25	25
5-(*p*-chlorobenzoyl)-N,N-diethyl-1-methylpyrrole-2-(N,N-diethyl)-acetamide	25	36
5-(*p*-chlorobenzoyl)-1-methylpyrrole-2-propionic acid	25	63
5-(*p*-chlorobenzoyl)-4-methylpyrrole-23-acetic acid	50	43
5-benzoyl-4-methylpyrrole-2-acetic acid	100	34

As anti-inflammatory agents, the compounds of formulas (I—a, b, c and d) and salts thereof are of value in reducing inflammation and alleviating the symptoms of rheumatic, arthritic and other inflammatory conditions. The compounds can be administered in therapeutic dosages in conventional pharmaceutical formulations for oral and parenteral administration, for example, tablets, capsules, solutions, suspensions or elixirs or in injectable form.

As is evident from the previously described methods of forming the subject compounds, many of the compounds of formulas (I—a, b, c and d) are also useful as intermediates in the syntheses of other compounds thereunder. For example, the nitriles and esters represented by formulas (IV, V, VI and VII) are useful intermediates in the syntheses of corresponding acids. In addition, the 5-nitrobenzoyl compounds of formulas (I—a) and (I—b) are useful intermediates in the transformation procedure to corresponding 5-aminobenzoyl compounds. Moreover, the acids embraced within formulas (I—a, b, c and d) are useful intermediates in the transformation procedures to corresponding esters, amides and basic salts.

The following examples are intended to illustrate, but not to limit, the scope of the present invention.

EXAMPLE I

Ethyl 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetate:

To a solution of 22.0 g. (0.131 mole) of ethyl N - methylpyrrole - 2 - acetate and 24.5 g. (0.14 mole) of *p*-chlorobenzoyl chloride in 120 ml. of carbon disulfide is added 35.0 g. (0.262 mole) of anhydrous aluminum chloride over a period of 20 minutes with intermittant cooling to keep the temperature at 25°C. The mixture is stirred for an additional 20 minutes. The carbon disulfide solvent is then decanted and discarded. The red gummy residue is washed with hexane and dilute hydrochloric acid and ice is added to the mixture. The mixture is extracted with ether. The ether solution is shaken with an aqueous solution of dimethylaminopropylamine and washed with dilute hydrochloric acid followed by brine. The solution is dried over magnesium sulfate and treated with charcoal. After removal of the charcoal, the solvent is evaporated *in vacuo* leaving a partially crystalline red oil as a residue. This material is extracted with three 500 ml. portions of boiling pentane. The combined pentane extracts are evaporated *in vacuo* and the residue is crystallized from 60 ml. of cold methanol. The resulting solid is collected and washed with cold methanol; there is obtained about 6.3 g. of white crystalline solid, ethyl 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole-2 - acetate, m.p. 74—76°C. Recrystallization from methyl cyclohexane raises the melting point to 78—80°C.

Analysis: Calcd. for $C_{14}H_{12}ClNO_3$: C, 60.54; H, 4.36; N, 5.05%
Found: C, 60.54; H, 4.37; N, 5.14%

EXAMPLE II

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole-2 - acetic acid and its sodium salt:

A suspension of 3.06 g. (0.01 mole) of ethyl - 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetate in 25 ml. of 0.5 N sodium hydroxide is refluxed for 30 minutes. About two-thirds of this solution is cooled, washed with ether, and then acidified with dilute hydrochloric acid. The resulting solid precipitate is collected by filtration, dried and recrystallized from ethanol-water to give the product, 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid; m.p. 189—191°C. Upon recrystallization from ethanol-water, the melting point is 188—190°C. The other one-third of the solution is cooled in an ice-bath whereupon the yellow sodium salt of the acid is precipitated and collected by filtration.

EXAMPLE III

By following the procedures of the foregoing examples, except that an equivalent quantity of benzoyl chloride is employed in place of the *p*-chlorobenzoylchloride used in Example I, there are obtained as respective products, ethyl 5 - benzoyl - 1 - methylpyrrole - 2 - acetate and 5 - benzoyl - 1-methyl - pyrrole - 2 - acetic acid.

EXAMPLE IV

5 - Benzoyl - 1 - methylpyrrole - 2 - acetonitrile:

To a chilled suspension of 9.7 g. (0.07 mole) of aluminum chloride in 45 ml. methylene chloride is added 9 ml. (0.07 mole) benzoyl chloride. The resulting solution is added dropwise to a solution of 1 - methylpyrrole - 2 - acetonitrile in 30 ml. methylene chloride while cooling externally with an ammonium chloride ice bath (temperature below 5°C.). After the addition is complete, the reaction mixture is stirred at 0°C. for fifteen minutes and then poured into ice acidified with 3N hydrochloric acid. The acidic fraction is extracted three times with methylene chloride. The organic fractions are combined and washed consecutively with N,N - dimethyl - 1,3 - propanediamine and 3N hydrochloric acid. The organic solution is dried over anhydrous magnesium sulfate. The solvent is then evaporated off to yield an oily residue which is column chromatographed on neutral alumina using hexane, benzene and ethyl-

acetate as successive solvents. The first few fractions having ultraviolet absorption in the 240—260 mμ range contain the desired product. These fractions are combined, the solvent evaporated off and the oily residue, when triturated with methanol, yields the crystalline product, 5 - benzoyl - 1 - methylpyrrole - 2-acetonitrile, m.p. 106—108°C.

EXAMPLE V

5 - Benzoyl - 1 - methylpyrrole - 2 - acetic acid:

A suspension of 2.42 g. (0.11 mole) of 5-benzoyl - 1 - methylpyrrole - 2 - acetonitrile, 0.9 g. (0.22 mole) sodium hydroxide, 6 ml. water, and 0.5 ml. ethanol, is stirred and refluxed for one hour. The resulting solution is cooled and extracted in water and chloroform. The aqueous fraction is made acidic with 3N hydrochloric acid. A white solid, 5-benzoyl - 1 - methylpyrrole - 2 - acetic acid, precipitates which is filtered and washed with a hexane-ether solution, m.p. 144—145°C.

Analysis: Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.30; N, 5.76%
Found: C, 69.23; H, 5.47; N, 5.78%

EXAMPLE VI

5 - (*m* - Chlorobenzoyl) - 1 - methylpyrrole-2 - acetonitrile:

To a cooled suspension of 16.6 g. (0.12 mole) aluminum chloride in 60 ml. 1,2-dichloroethane is added dropwise 23 g. (0.12 mole) *m*-chlorobenzoylchloride. The resulting suspension is added dropwise to a cooled solution of 15 g. (0.12 mole) 1-methylpyrrole-2-acetonitrile in 60 ml. 1,2-dichloroethane. The reaction mixture is stirred for about twenty minutes at room temperature and then heated and refluxed for three minutes. The reaction is terminated by pouring the mixture into ice acidified with 3N hydrochloric acid. The resulting two fractions are separated. The aqueous fraction is washed with chloroform. The organic fractions are combined and washed consecutively with N,N-dimethyl - 1,3 - propanediamine, 3N hydrochloric acid and saturated sodium chloride solution. The organic fraction is then dried over anhydrous magnesium sulfate. The solvent is evaporated and the resulting residue is triturated with cold methanol to yield a precipitate of the desired product which is filtered off and set aside. The methanol filtrate is concentrated *in vacuo* and the remaining oily residue is chromatographed on a column packed with neutral alumina using hexane, benzene and ether as the successive solvents. About 2.5 g. of the desired product are isolated by evaporation of the first few compound-bearing (ether) fractions. The solids are combined and recrystallized from methanol to yield about 3.6 g. of 5 - (*m* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile, m.p. 122—127°C.

Analysis: Calcd. for $C_{14}H_{11}ClN_2O$: N, 10.83%
Found: N, 10.52%

EXAMPLE VII

5 - (*m* - Chlorobenzoyl) - 1 - methylpyrrole-2 - acetic acid:

A mixture of 2.8 g. (0.01 mole) of 5 - *m*-chlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile, 22 ml. of 1N sodium hydroxide solution and 5 ml. ethanol is stirred at reflux for 15 hours. Some of the ethanol is evaporated. The remaining solution is poured into ice acidified with dilute hydrochloric acid. A white solid, 5 - (*m* - chlorobenzoyl) - 1-methylpyrrole - 2 - acetic acid, precipitates which is recrystallized twice from methanol/water mixture, m.p. 165°C.

Analysis: Calcd. for $C_{14}H_{12}ClNO_3$: C, 60.54; H, 4.36; N, 5.05%
Found: C, 60.61; H, 4.40; N, 4.87%

EXAMPLE VIII

A. The procedure of Example VI is repeated except that an equivalent quantity of *p* - bromobenzoyl chloride and *p* - fluorobenzoyl chloride is used in place of the *m*-chlorobenzoyl chloride used therein to yield, as respective products:

5 - (*p* - bromobenzoyl) - 1 - methylpyrrole-2 - acetonitrile, m.p. 139—141°C; and
5 - (*p* - fluorobenzoyl) - 1 - methylpyrrole-2 - acetonitrile, m.p. 134—136°C.

B. By following the procedure of Example VII, using an equivalent quantity of the fore-

going acetonitriles in place of the 5 - (*m*-chlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile used therein, the following respective acids are obtained:

5 - (*p* - bromobenzoyl) - 1 - methylpyrrole-2 - acetic acid, m.p. 188°C; and
5 - (*p* - fluorobenzoyl) - 1 - methylpyrrole-2 - acetic acid, m.p. 164—165°C.

EXAMPLE IX

5 - (*o* - Chlorobenzoyl) - 1 - methylprrole-2 - acetonitrile:

To a cooled suspension of 14 g. (0.105 mole) aluminum chloride in 45 ml. dichloroethane is added dropwise, 18.5 g. (0.105 mole) *o*-chlorobenzoyl chloride. The resulting solution is added dropwise to a cooled (0°C.) solution of 1 - methylpyrrole - 2 - acetonitrile in 45 ml. dichloroethane keeping the temperature at approximately 10°C. The mixture is stirred at room temperature for about twenty minutes, and then refluxed for three minutes. It is poured into ice acidified with 3N hydrochloric acid and the resulting two layers are separated. The aqueous fraction is extracted twice with chloroform. The organic fractions are combined and washed twice with N,N-dimethyl - 1,3 - propanediamine, once with 3N hydrochloric acid and once with saturated sodium chloride solution. The organic fraction is dried over anhydrous magnesium sulfate. The solvent is evaporated and the resulting oil is chromatographed on a column packed with neutral alumina using benzene and ether as successive solvents. The first compound-bearing fractions contain the desired product. The solvent is evaporated and the resulting oil crystallizes upon treatment with methanol. The solid product, 5 - (*o* - chlorobenzoyl)-1 - methylpyrrole - 2 - acetonitrile, is purified by recrystallization from benzene: cyclohexane solution, m.p. 80—85°C.

Analysis: Calcd. for $C_{14}H_{12}ClNO_3$: C, 60.54; H, 4.36; N, 5.05%
Found: C, 60.55; H, 4.43; N, 4.91%

EXAMPLE X

5 - (*o* - Chlorobenzoyl) - 1 - methylpyrrole-2 - acetic acid:

A solution of 2.4 g. (0.009 mole) - 5 - (*o*-chlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile, 18 ml. of 1N sodium hydroxide and 18 ml. 95% ethanol is stirred and refluxed for seven hours. The ethanol is evaporated off and the remaining solid residue is dissolved in water and washed with chloroform. The aqueous layer is made acidic with 3N hydrochloric acid. An oil precipitate which crystallizes when scratched. The solid is filtered and washed with water and hexane. The solid is purified by recrystallization from methanol: water and again from ether: hexane, m.p. 140—141°C.

EXAMPLE XI

5 - (2',4' - Dichlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile:

To a suspension of 16.6 g. (0.125 mole) of aluminum chloride in 60 ml. 1,2 - dichloroethane is added 26.2 g. (0.125 mole) of 2,4-dichlorobenzoyl chloride. The resulting solution is added slowly to a solution of 15 g. (0.125 mole) of 1 - methylpyrrole - 2 - acetonitrile in 60 ml. 1,2 - dichloroethane while cooling externally with an ice bath. After the addition is complete, the mixture is stirred for forty minutes at room temperature followed by heating at reflux for three minutes. It is then poured into ice acidified with dilute hydrochloric acid. The organic phase is separated and washed successively with N,N - dimethyl - 1,3 - propanediamine, 3N hydrochloric acid, and saturated sodium chloride solution. It is then dried over magnesium sulfate and the solvent evaporated. The resulting red oily residue is chromatographed on a column packed with neutral alumina and eluted with benzene and ether. The first compound-bearing fractions upon evaporation yield a white solid, 5 - (2',4' - dichlorobenzoyl) - 1-methylpyrrole - 2 - acetonitrile, which is purified by recrystallization from methanol, m.p. 129—130°C.

Analysis: Calcd. for $C_{14}H_{10}Cl_2N_2O$: N, 9.56%
Found: N, 9.51%

EXAMPLE XII

5 - (2',4' - Dichlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid:

A solution of 4.3 g. (0.015 mole) of 5-(2',4' - dichlorobenzoyl) - 1 - methylpyrrole-2 - acetonitrile in 30 ml. 1N sodium hydroxide and 30 ml. 95% ethanol is refluxed overnight. The solution is concentrated and poured into dilute hydrochloric acid. A white solid, 5-(2',4' - dichlorobenzoyl) - 1 - methylpyrrole-2 - acetic acid precipitates which is recrystallized from isopropanol and methanol, m.p. 165—166°C.

Analysis: Calcd. for $C_{14}H_{11}Cl_2NO_3$: C, 53.86; H, 3.55; N, 4.68%
Found: C, 53.97; H, 3.66; N, 4.69%

EXAMPLE XIII

5 - (*p* - Toluoyl) - 1 - methylpyrrole - 2-acetonitrile:

To a cooled suspension of 26.6 g. (0.2 mole) aluminum chloride in 80 ml. dichloroethane is added dropwise 30.8 g. (0.2 mole) *p*-toluoyl chloride. The resulting solution is added dropwise to a solution of 1 - methylpyrrole - 2-acetonitrile in 80 ml. dichloroethane cooled externally with an ice bath. After the addition, the resulting solution is stirred at room temperature for twenty minutes and then refluxed for three minutes. The solution is poured into ice acidified with dilute hydrochloric acid. The organic and aqueous fractions are separated. The aqueous fraction is extracted once with chloroform. The organic fractions are combined and washed successively with N,N - dimethyl - 1,3 - propanediamine, dilute hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution. The organic fraction is dried over anhydrous magnesium sulfate. The solvent is then evaporated off. Upon trituration of the residue with methanol, a solid crystallizes, 5 - (*p* - toluoyl) - 1 - methylpyrrole - 2 - acetonitrile, which is removed by filtration and purified by recrystallization from benzene. Additional product is isolated from the mother liquors which are combined, concentrated *in vacuo* and the resulting oily residue column chromatographed on neutral alumina using hexane, benzene and ether as successive solvents. The product is isolated by concentrating *in vacuo* the first few major compound-bearing fractions (10% ether in benzene). The solids are combined and recrystallized from methanol and then from benzene-hexane, m.p. 102—105°C.

EXAMPLE XIV

5 - (*p* - Toluoyl) - 1 - methylpyrrole - 2-acetic acid:

A solution of 3.67 g. (0.015 mole) of 5-(*p* - toluoyl) - 1 - methylpyrrole - 2 - acetonitrile, 24 ml. of 1N sodium hydroxide, and 50 ml. of 95% ethanol is stirred and refluxed for twenty-four hours. The resulting solution is poured into ice acidified with dilute hydrochloric acid. A white solid precipitates which is extracted into ether. The ether phase is washed with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent is evaporated and a white solid, 5 - (*p* - toluoyl) - 1 - methylpyrrole-2 - acetic acid, is obtained which is recrystallized twice from isopropanol, m.p. 155—157°C.

EXAMPLE XV

A. By repeating the procedure of Example XI, except that an equivalent quantity of *o*-toluoyl chloride, *m*-toluoyl chloride, *p*-ethylbenzoyl chloride and 3,4-dimethylbenzoyl chloride is used in lieu of the 2,4-dichlorobenzoyl chloride used therein, there are obtained as respective products the corresponding 5 - (*o* - toluoyl), 5 - (*m* - toluoyl), 5-(*p* - ethylbenzoyl) and 5 - (3',4' - dimethylbenzoyl) derivatives of 1 - methylpyrrole - 2-acetonitrile.

B. The procedure of Example XII is repeated, using an equivalent quantity of each of the foregoing acetonitriles in place of the 5 - (2',4' - dichlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile used therein, to yield as respective products the corresponding 5-(*o* - toluoyl), 5 - (*m* - toluoyl), 5 - (*p* - ethylbenzoyl) and 5 - (3',4' - dimethylbenzoyl) derivatives of 1 - methylpyrrole - 2 - acetic acid.

EXAMPLE XVI

Methyl 5 - (*p* - anisoyl) - 1 - methylpyrrole-2 - acetate:

A solution of 17.0 g. (0.1 mole) of *p*-anisoyl chloride and 13.3 g. (0.1 mole) of aluminum chloride in 200 ml. of methylene chloride is added over 5 minutes to a solution of methyl 1 - methylpyrrole - 2 - acetate in 100 ml. of methylene chloride at ice bath temperature. The mixture is stirred for 25 minutes and poured into ice acidified with dilute hydrochloric acid. The organic layer is separated and the aqueous layer is washed with methylene chloride. The combined organic solutions are washed successively with dimethylaminopropylamine solution, dilute hydrochloric acid and brine and then dried over anhydrous magnesium sulfate. The solvent is evaporated *in vacuo* to give a dark oily residue which is crystallized from 40 ml. of cold methanol. The solid is collected by filtration, washed with cold methanol and recrystallized from methanol to give white crystalline methyl 5 - (*p* - anisoyl) - 1 - methylpyrrole - 2 - acetate, m.p. 104—105°C.

EXAMPLE XVII

5 - (*p* - Anisoyl) - 1 - methylpyrrole - 2 - acetic acid:

A solution of 3.00 g. (0.0105 mole) of methyl 5 - (*p* - anisoyl) - 1 - methylpyrrole-2 - acetate in 12 ml. (0.012 mole) of 1N sodium hydroxide solution and 5 ml. of 95% ethanol is refluxed for 30 minutes. The solution is diluted with water and the ethanol is evaporated *in vacuo*. The solution is filtered and the filtrate acidified with dilute hydrochloric acid. The precipitated solid is collected by filtration, dried and recrystallized from methanol-water to give about 2.4 g. (87% yield) of white 5 - (*p* - anisoyl) - 1-methylpyrrole - 2 - acetic acid, m.p. 170—171°C.

Analysis: Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13%
Found: C, 66.01; H, 5.62; N, 5.12%

EXAMPLE XVIII

By repeating the procedure of Examples XVI and XVII successively, except that an equivalent quantity each of *m*-anisoyl chloride and p-ethoxybenzoyl chloride is initially employed in place of *p*-anisoyl chloride, there are obtained as ester products, the corresponding 5 - (*m* - anisoyl) and 5 - (*p* - ethoxybenzoyl) derivatives of methyl 1 - methylpyrrole - 2-acetate, and as acid products, the corresponding 5 - (*m* - anisoyl) and 5 - (*p* - ethoxybenzoyl) derivatives of 1 - methylpyrrole - 2-acetic acid, respectively.

EXAMPLE XIX

5 - (*m* - Chloro - *p* - toluoyl) - 1 - methylpyrrole - 2 - acetonitrile:

21.4 Grams (0.114 mole) of 3 - chloro-4 - methylbenzoylchloride is added to a suspension of 15.2 g. (0.114 mole) aluminum chloride in 50 ml. 1,2-dichloroethane. The resulting solution is added dropwise to a chilled solution of 13.7 g. (0.114 mole) of 1-methylpyrrole - 2 - acetonitrile in 50 ml. 1,2-dichloroethane. After the addition is complete, the mixture is stirred for ten minutes at room temperature and then heated to reflux for three minutes. It is poured into ice acidified with dilute HCl. The organic phase is separated and washed consecutively with N,N-dimethyl - 1,3 - propanediamine, 3N hydrochloric acid and saturated sodium chloride solution. It is then dried over anhydrous magnesium sulfate and the solvent evaporated off. A white solid, 5 - (*m* - chloro - p - toluoyl)-1 - methylpyrrole - 2 - acetonitrile, precipitates from the resulting oily residue upon trituration with methanol which is purified by recrystallization from methanol, m.p. 116—118°C.

Analysis: Calcd. for $C_{15}H_{13}ClN_2O$: N, 10.26%
Found: N, 10.38%

EXAMPLE XX

5 - (*m* - Chloro - *p* - toluoyl) - 1 - methylpyrrole - 2 - acetic acid:

A solution of 3.5 g. (0.0013 mole) of 5-(*m* - chloro - *p* - toluoyl) - 1 - methylpyrrole-2 - acetonitrile in 18 ml. 95% ethanol and 26 ml. 1N sodium hydroxide is heated at reflux overnight. The reaction mixture is then cooled and poured into dilute hydrochloric acid. The resulting white precipitate 5 - (*m*-chloro - *p* - toluoyl) - 1 - methylpyrrole - 2-acetic acid, is filtered off and purified by recrystallization once from isopropanol, m.p. 176—178°C.

EXAMPLE XXI

By repeating the Friedel-Crafts procedure of Example XVI with an equivalent amount of an appropriately substituted benzoyl chloride, the following 5-aroyl derivatives of methyl 1 - methylpyrrole - 2 - acetate are obtained:

methyl 5 - (3',4' - dimethoxybenzoyl) - 1-methylpyrrole - 2 - acetate;
methyl 5 - (3',5' - dinitrobenzoyl) - 1-methylpyrrole - 2 - acetate;
methyl 5 - (3' - bromo - 4' - chlorobenzoyl)-1 - methylpyrrole - 2 - acetate;
methyl 5 - (2',3',5' - tribromobenzoyl) - 1-methylpyrrole - 2 - acetate; and
methyl 5 - (3',4',5' - trimethoxybenzoyl) - 1-methylpyrrole - 2 - acetate.

EXAMPLE XXII

The transformation of an acetic acid ester function to an acetic acid function according to the hydrolysis procedure of Example XVII is repeated with an equivalent amount of each of the pyrrole-acetates obtained in Example XXI to yield, as respective products, the corresponding 5 - aroyl - 1 - methylpyrrole - 2-acetic acids.

EXAMPLE XXIII

5 - (*p* - Nitrobenzoyl) - 1 - methylpyrrole-2 - acetonitrile:

A solution of 46.4 g. (0.25 mole) of *p*-nitrobenzoyl chloride in 100 ml. 1,2 - dichloroethane is added portionwise to a suspension of 32.2 g. (0.25 mole) aluminum chloride in 100 ml. 1,2-dichloroethane. This mixture is added dropwise to a chilled solution of 30.0 g. (0.25 mole) 1 - methylpyrrole - 2-acetonitrile in 100 ml. 1,2 - dichloroethane. After the addition is complete, the mixture is stirred for twenty minutes at room temperature and then refluxed for four minutes. It is poured into ice acidified with 3N hydrochloric acid. The organic phase is separated and washed successively with N,N - dimethyl-1,3 - propanediamine, 3N hydrochloric acid and saturated sodium chloride solution. It is then dried over magnesium sulfate and the solvent evaporated *in vacuo*. The resulting semi-solid residue is triturated with cold methanol from which the product, 5 - (*p*-nitrobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile, crystallizes. It is removed by filtration and purified by recrystallization from acetone, m.p. 167—169°C.

EXAMPLE XXIV

5 - (*p* - Aminobenzoyl) - 1 - methylpyrrole-2 - acetonitrile:

A solution of 7 g. (0.026 mole) of 5 - (*p*-nitrobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile in 450 ml. of ethyl acetate containing 1 g. palladium-on-carbon catalyst is hydrogenated in a Parr shaker under 44 p.s.i. of

hydrogen until the theoretical amount of hydrogen is consumed. The catalyst is filtered off and the solvent evaporated *in vacuo*. About 6.0 g. (97% yield) of a yellow solid, 5 - (*p*-aminobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile remains, m.p. 137—142°C.

EXAMPLE XXV

5 - (*p* - Aminobenzoyl) - 1 - methylpyrrole-2 - acetic acid:

A suspension of 6.0 g. (0.025 mole) of 5-(*p* - aminobenzoyl) - 1 - methylpyrrole - 2-acetonitrile, 25 ml. 95% ethanol and 25 ml. 1N sodium hydroxide is refluxed overnight. The ethanol is then evaporated *in vacuo* and the remaining suspension is poured into ice acidified with dilute hydrochloric acid to pH 5. The resulting solid is partitioned between sodium bicarbonate solution and chloroform. The insoluble substances are filtered from the two-phase mixture. The sodium bicarbonate layer is separated and acidified slowly with dilute hydrochloric acid. Solids precipitate at various pHs which are separated by filtration. The desired product, 5 - (*p* - aminobenzoyl)-1 - methylpyrrole - 2 - acetic acid, precipitates at pH 3, m.p. 173—175°C.

EXAMPLE XXVI

Ethyl 5 - (*p* - Nitrobenzoyl) - 1 - methylpyrrole - 2 - acetate:

A solution of 5.5 g. (0.03 mole) of *p*-nitrobenzoyl chloride in 60 ml. methylene chloride is added to a suspension of 3.9 g. (0.03 mole) aluminum chloride in 20 ml. methylene chloride. The resulting suspension is added dropwise to a chilled (—15°C.) solution of ethyl 1 - methylpyrrole - 2 - acetate in 50 ml. methylene chloride. The solution is stirred for 15 minutes at —10°C. and at room temperature for 15 minutes. The reaction mixture is poured into ice-dilute hydrochloric acid. The organic phase is separated and washed successively with N,N - dimethyl - 1,3-propanediamine, 3N hydrochloric acid and a saturated solution of sodium chloride, dried over anhydrous magnesium sulfate, and the solvent evaporated *in vacuo*. A solid, ethyl 5 - (*p* - nitrobenzoyl) - 1 - methylpyrrole-2 - acetate, crystallizes from the remaining oily residue which is isolated by recrystallization from methanol, m.p. 103—106°C.

EXAMPLE XXVII

5 - (*p* - Nitrobenzoyl) - 1 - methylpyrrole-2 - acetic acid:

A solution of 3.2 g. (0.01 mole) of ethyl 5 - (*p* - nitrobenzoyl) - 1 - methylpyrrole-2 - acetate and 25 ml. ethanol is brought to reflux. To this is added dropwise 10 ml. of 1N sodium hydroxide solution. After the addition is complete, the ethanol is evaporated and the residue is acidified with dilute hydrochloric acid. The resulting solid, 5 - (*p*-nitrobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, is separated by filtration and purified by recrystallization from ethanol, m.p. 192—195°C.

EXAMPLE XXVIII

Ethyl 5 - (*p* - cyanobenzoyl) - 1 - methylpyrrole - 2 - acetate:

A solution of 5.0 g. (0.03 mole) of *p*-cyanobenzoyl chloride in 60 ml. of methylene chloride is added to a suspension of 40 g. of aluminum chloride in 30 ml. methylene chloride. The resulting mixture is added dropwise to a chilled solution of 5.0 g. (0.03 mole) of ethyl 1 - methylpyrrole - 2 - acetate in 15 ml. of methylene chloride. The resulting mixture is stirred at room temperature for 20 minutes, and then poured into ice acidified with dilute hydrochloric acid. The organic phase is separated, washed successively with N,N-dimethylaminopropylamine, 3N hydrochloric acid and brine, and dried over anhydrous magnesium sulfate. The solvent is evaporated *in vacuo*. The resulting solid, which separates from the oily residue on standing, is recrystallized from methanol to give pure ethyl 5 - (*p* - cyanobenzoyl) - 1 - methylpyrrole - 2 - acetate, m.p. 117—120°C.

EXAMPLE XXIX

5 - (*p* - Cyanobenzoyl) - 1 - methylpyrrole-2 - acetic acid:

A solution of 0.5 g. (0.0017 mole) of ethyl 5 - (*p* - cyanobenzoyl) - 1 - methylpyrrole-2 - acetate in 3 ml. ethanol is brought to reflux and 1.7 ml. of 1N sodium hydroxide solution is added dropwise. The mixture is refluxed for 3 minutes and the ethanol is then evaporated *in vacuo*. The residue is diluted with water and acidified with dilute hydrochloric acid. A white solid precipitates, 5 - (*p* - cyanobenzoyl) - 1 - methylpyrrole-2 - acetic acid, which is collected by filtration and dried, m.p. 196—198°C.

EXAMPLE XXX

Methyl 5 - (*p* - methylthiobenzoyl) - 1-methylpyrrole - 2 - acetate is obtained by repeating the procedure of Example XVI except that an equivalent quantity of *p*-methylthiobenzoyl chloride is used in place of the *p*-anisoyl chloride used therein.

EXAMPLE XXXI

5 - (*p* - Methylthiobenzoyl - 1 - methylpyrrole - 2 - acetic acid is obtained by repeating the hydrolysis procedure of Example XVII except that the hydrolysis is performed on an equivalent amount of the ester obtained from Example XXX.

EXAMPLE XXXII

Ethyl 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - (*α* - methyl) - acetate:

A solution of 6.68 g. (0.0219 mole) of ethyl 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole-2 - acetate in 50 ml. of ether is added to a

solution of 0.94 g. (0.024 mole) of sodamide in about 150 ml. of liquid ammonia at −33°C. The mixture is allowed to reflux for 15 minutes and 3.10 g. (0.0219 mole) of methyl iodide is added. The mixture is stirred for one hour; then the ammonia is allowed to boil off. Ether and enough ammonium chloride to neutralize any anion are added. The mixture is poured into dilute hydrochloric acid and the ether solution is separated and washed with sodium bisulfite solution, sodium bicarbonate solution and brine. It is dried over anhydrous magnesium sulfate and evaporated to give about 6.8 g. of an oily residue which crystallizes upon standing. The solid is recrystallized successively from cyclohexane and methanol to give a white crystalline solid, ethyl 5 - (*p* - chlorobenzoyl) - 1-methylpyrrole - 2 - (α - methyl) - acetate, m.p. 67—68°C.

EXAMPLE XXXIII

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole-2 - (α - methyl) - acetic acid:

A solution of 4.05 g. (0.0126 mole) of ethyl 5 - (*p* - chlorobenzoyl) - α - methyl - 1-methylpyrrole - 2 - acetate, 15 ml. of 1N sodium hydroxide solution and 2 ml. of ethanol is refluxed for 30 minutes. The solution is cooled, diluted with water and filtered. The filtrate is acidified with dilute hydrochloric acid. The precipitated solid is collected and recrystallized from methanol-water to give a white crystalline solid, 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - (α - methyl)-acetic acid, m.p. 135—136°C.

Analysis: Calcd. for $C_{13}H_{14}ClNO_3$: C, 61.76; H, 4.83; N, 4.82%
Found: C, 61.68; H, 4.86; N, 4.89%

EXAMPLE XXXIV

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole-2 - (α - methyl) - acetonitrile:

To a suspension of sodium hydride (12.2 g. of 50% w/w NaH in mineral oil) in 1,2-dimethoxyethane is added 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile (62.6 g., 0.24 mole) in 1,2-dimethoxyethane over a period of ½ hr. at room temperature. After the addition is complete, the mixture is stirred for 1 hour and then 35 g. (0.25 mole) of methyl iodide is added. The reaction mixture is stirred for an additional 3 hrs., concentrated under reduced pressure, diluted with water and extracted with chloroform. After drying, the chloroform is removed leaving a brown solid residue which is triturated with cold methanol to give yellow crystals of 5-(*p* - chlorobenzoyl) - 1 - methylpyrrole - 2-(α - methyl) - acetonitrile, m.p. 145—148°C. Two recrystallizations from methanol raises the m.p. to 151.5—152.5°C.

EXAMPLE XXXV

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole-2 - (α - methyl) - acetic acid:

A 27.1 g. (0.1 mole) sample of 5 - (*p*-chlorobenzoyl) - α - methyl - 1 - methylpyrrole - 2 - acetonitrile is hydrolyzed by refluxing for 16 hours with 8g. (0.2 mole) of sodium hydroxide in 350 ml. of aqueous ethanol. Upon concentration *in vacuo*, the sodium salt separates, is filtered off and dissolved in water. After acidification with dilute HCl, the corresponding acid, 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - (α - methyl)-acetic acid, precipitates. The original basic filtrates are also acidified, extracted with chloroform and concentrated. The residual solid is combined with the previous solid and recrystallized from methanol-water to give the pure product, 5 - (*p* - chlorobenzoyl) - 1-methylpyrrole 2 - (α - methyl) - acetic acid, m.p. 139—141°C.

EXAMPLE XXXVI

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole - (α - ethyl) - acetic acid:

A solution of 6.5 g. (0.021 mole) of ethyl 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole-2 - acetate in 60 ml. of ether is added to a suspension of 1.25 g. (0.032 mole) of sodamide in 150 ml. of refluxing liquid ammonia. After 10 minutes, 4.98 g. (0.032 mole) of ethyl iodide are added. The mixture is stirred for 1.5 hrs. and an additional 1.0 g. (.0064 mole) of ethyl iodide is added. Stirring is continued for 30 minutes and ammonium chloride is then added to neutralize any anions. The mixture is allowed to warm to room temperature and the ammonia allowed to escape. Ether is added and the mixture poured into dilute hydrochloric acid. The ether layer is separated and the aquous layer is washed with ether. The combined ether solutions are washed successively with sodium bisulfite solution and brine and then dried over anhydrous magnesium sulfate. The solvent is evaporated *in vacuo* to give about 7.4 g. of a yellow oily residue containing ethyl 5 - (*p*-chlorobenzoyl) - 1 - methylpyrrole - 2 (α-ethyl) - acetate, which is used as such in the following transformation to acid procedure.

A 6.9 g. sample of the oily residue is dissolved in 30 ml. of ethanol and 11.4 ml. of 1N sodium hydroxide is added. The mixture is refluxed for 1 hr. The solvent is then evaporated *in vacuo* and the residue partitioned between ether and water. The aqueous layer is separated and acidified with dilute hydrochloric acid. The precipitated oil, which is separated, crystallizes on scratching to give a solid, 5 - (*p* - chlorobenzoyl) - 1 - methyl-

pyrrole - 2 - (α - ethyl) - acetic acid, which is collected and dried, m.p. 108—112°C. After successive recrystallizations from ether-methylcyclohexane, benzene-hexane, methylcyclohexane and ether-hexane, the m.p. is 110—114°C.

Analysis: Calcd. for $C_{16}H_{16}ClNO_3$: C, 62.84; H, 5.27; N, 4.58%
Found: C, 63.01; H, 5.36; N, 4.61%

EXAMPLE XXXVII

The alkylation and ester-to-acid transformation procedures of Example XXXVI are repeated except that an equivalent amount of an appropriate 5 - aroyl - 1 - methylpyrrole-2 - acetic acid alkyl ester and an equivalent amount of an appropriate alkyl halide alkylating agent are employed to yield the following products:

5 - benzoyl - 1 - methylpyrrole - 2 - [α-(n - butyl)] - acetic acids;
5 - (p - methoxybenzoyl) - 1 - methylpyrrole-2 - (α - methyl) - acetic acid;
5 - benzoyl - 1 - methylpyrrole - 2 - [α - n-propyl)] - acetic acid; and
5 - (p - cyanobenzoyl) - 1 - methylpyrrole-2 - (α - methyl) - acetic acid.

EXAMPLE XXXVIII

The alkylation and nitrile-to-acid transformation procedures of Examples XXXIV and XXXV, respectively, are repeated except that an equivalent amount of an appropriate 5 - aroyl - 1 - methylpyrrole - 2 - acetonitrile and an equivalent amount of an appropriate alkyl halide alkylating agent are employed to yield the following products:

5 - (m - chlorobenzoyl) - 1 - methylpyrrole-2 - (α - methyl) - acetic acid;
5 - (p - fluorobenzoyl) - 1 - methylpyrrole-2 - (α - ethyl) - acetic acid;
5 - (p - methylbenzoyl) - 1 - methylpyrrole-2 - (α - ethyl) - acetic acid;
5 - (2',4' - dichlorobenzoyl) - 1 - methylpyrrole - 2 - (α - methyl) - acetic acid; and
3 - (3' - chloro - 4' - methylbenzoyl) - 1-methylpyrrole - 2 - (α - ethyl) - acetic acid.

EXAMPLE XXXIX

5 - (p - Chlorobenzoyl) - pyrrole - 2 - acetonitrile:

To a chilled suspension of 26.80 g. (0.2 mole) of aluminum chloride in 110 ml. of methylene chloride is added dropwise 35 g. (0.2 mole) of p-chlorobenzoyl chloride. The mixture is added dropwise to a solution of 21.22 g. (0.2 mole) of pyrrole - 2 - acetonitrile in 125 ml. methylene chloride which is cooled externally with an ammonium chloride ice bath. After addition is complete, the reaction mixture is stirred for ten minutes at 0°C. and then poured into ice acidified with dilute hydrochloric acid. A solid precipitates, 5 - (p - chlorobenzoyl) - pyrrole - 2 - acetonitrile, which is filtered off, washed with hot methanol and dried, m.p. 203—205°C.

EXAMPLE XL

5 - (p - Chlorobenzoyl) - pyrrole - 2 - acetic acid:

A solution of 3.6 g. (0.015 mole) of 5 - (p-chlorobenzoyl) - pyrrole - 2 - acetonitrile, 30 ml. 1N sodium hydroxide solution, and 30 ml. 95% ethanol is refluxed and stirred for 6 hours. The ethanol is evaporated off *in vacuo*. The resulting solid is dissolved in water and the solution filtered from insolubles. The filtrate is acidified with dilute hydrochloric acid. A white solid precipitates, 5 - (p - chlorobenzoyl) - pyrrole - 2 - acetic acid, which is purified by recrystallization from acetone: water (1:1), m.p. 210°C.

EXAMPLE XLI

The procedure of Example XXXIX is followed to prepare 5 - aroyl - 1 - R_1 - pyrrole-2 - acetonitriles wherein R_1 is hydrogen, except that an equivalent amount of an appropriate benzoyl chloride is used in place of the p-chlorobenzoyl chloride used therein, the following pyrrole-acetonitriles are obtained as respective products:

5 - Benzoyl - pyrrole - 2 - acetonitrile;
5 - (p - fluorobenzoyl) - pyrrole - 2 - acetonitrile;
5 - (p - methylbenzoyl) - pyrrole - 2 - acetonitrile;
5 - (p - methoxybenzoyl) - pyrrole - 2 - acetonitrile;
5 - (3' - chloro - 4 ' - methylbenzoyl)-pyrrole - 2 - acetonitrile; and
5 - (2',4' - dichlorobenzoyl) - pyrrole - 2-acetonitrile.

EXAMPLE XLII

The procedure of Example XI is repeated using an equivalent amount of each pyrrole-acetonitrile obtained in Example XLI in place of 5 - (p - chlorobenzoyl) - pyrrole - 2 - acetonitrile to yield, as respective products:

5 - benzoyl - pyrrole - 2 - acetic acid;
5 - (p - fluorobenzoyl) - pyrrole - 2 - acetic acid;
5 - (p - methylbenzoyl) - pyrrole - 2 - acetic acid;

5 - (*p* - methoxybenzoyl) - pyrrole - 2 - acetic acid;
5 - (3' - chloro - 4' - methylbenzoyl) - pyrrole-2 - acetic acid; and
5 - (2',4' - dichlorobenzoyl) - pyrrole - 2-acetic acid.

EXAMPLE XLIII

5 - (*p* - Chlorobenzoyl) - 1 - ethylpyrrole - 2-acetonitrile:

A mixture of 24.4 g. (0.1 mole) 5 - (*p*-chlorobenzoyl) - pyrrole - 2 - acetonitrile, 41.7 g. (0.3 mole) of potassium carbonate and 16.1 g. (0.105 mole) of ethyl iodide in 300 ml. of methylethylketone is refluxed overnight. The reaction mixture is then poured into water and extracted with chloroform. The organic solutions are combined, dried over anhydrous magnesium sulfate and the solvent evaporated *in vacuo*. The residue is crystallized from 2-propanol to give about 13 g. of solid crude product. The solid is sublimed overnight at 140°C. and 0.025 mm. Hg. The sublimate is successively recrystallized from 2-propanol, benzene and hexane to give 5 - (*p*-chlorobenzoyl) - 1 - ethylpyrrole - 2 - acetonitrile as a white solid, m.p. 145—147°C.

Analysis: Calcd. for $C_{15}H_{13}ClN_2O$: N, 10.27%
Found: N, 10.54%

EXAMPLE XLIV

5 - (*p* - Chlorobenzoyl) - 1 - ethylpyrrole-2 - acetic acid:

A suspension of 3.52 g. (0.013 mole) of 5-(*p* - chlorobenzoyl) - 1 - ethylpyrrole - 2-acetonitrile in 26 ml. of 1N sodium hydroxide and 50 ml. of ethanol is refluxed for six hours. The mixture is then diluted with water and cooled. A solid precipitates which is filtered off and set aside. The ethanol is evaporated from the filtrate *in vacuo*. The collected precipitate is added to the concentrated filtrate and the mixture is extracted with chloroform. The aqueous phase is separated, acidified with dilute hydrochloric acid, and the resulting precipitate (A) is collected by filtration and dried. The chloroform phase is evaporated and the residue refluxed with 12 ml. of 1N sodium hydroxide and 24 ml. of ethanol for 6 hours. The ethanol is evaporated *in vacuo* and the remaining solution is diluted with water and washed with chloroform. The aqueous solution is acidified with dilute hydrochloric acid and the precipitated solid (B) is collected and dried. The two samples of acidic material (A and B) are combined and recrystallized from aqueous isopropanol to give 5 - (*p* - chlorobenzoyl) - 1 - ethylpyrrole - 2-acetic acid as a white solid, m.p. 149—153°C.

Analysis: Calcd. for $C_{15}H_{14}ClNO_3$: C, 61.75; H, 4.83; N, 4.80%
Found: C, 61.78; H, 4.94; N, 4.96%

EXAMPLE XLV

The N-alkylation procedure of Example XLIII is followed to prepare 5 - aroyl - 1-R_1 - pyrrole - 2 - acetonitriles wherein R_1 is lower alkyl. By repeating such procedure with an equivalent amount of an appropriate N-unsubstituted 5 - aroyl - pyrrole - 2 - acetonitrile and an equivalent amount of an appropriate alkyl halide as the N-alkylating agent, the following respective products are obtained:

5 - benzoyl - 1 - ethylpyrrole - 2 - acetonitrile;
5 - (*p* - methylbenzoyl) - 1 - (*n* - propyl)-pyrrole - 2 - acetonitrile;
5 - (*p* - methoxybenzoyl) - 1 -ethylpyrrole-2 - acetonitrile; and
5 - (2',4' - dichlorobenzoyl) - 1 - (*n* - butyl)-pyrrole - 2 - acetonitrile.

EXAMPLE XLVI

The nitrile-to-acid transformation procedure of Example XLIV is repeated, except that an equivalent amount of each acetonitrile obtained in Example XLV is used as the starting acetonitrile to yield the following respective products:

5 - benzoyl - 1 - ethylpyrrole - 2 - acetic acid;
5 - (*p* - methylbenzoyl) - 1 - (*n* - propyl)-pyrrole - 2 - acetic acid;
5 - (*p* - methoxybenzoyl) - 1 - ethylpyrrole-2 - acetic acid; and
5 - (2',4' - dichlorobenzoyl) - 1 - (*n* - butyl)-pyrrole - 2 - acetic acid.

EXAMPLE XLVII

The alkylation and transformation procedures of Examples XXXIV and XXXV, respectively, are repeated, except that an equivalent amount of each alkylpyrrole-acetonitrile obtained in Examples XLIII and XLV is used in place of the starting acetonitrile used in Example XXXIV, and an equivalent amount of an appropriate alkyl halide is used as the alkylating agent, to yield the following respective products:

5 - (*p* - chlorobenzoyl) - 1 - ethylpyrrole-2 - *α* - methyl) - acetic acid;
5 - benzoyl - 1 - ethylpyrrole - 2 - (*α*-methyl) - acetic acid;
5 - (*p* - methylbenzoyl) - 1 -(*n* - propyl)-pyrrole - 2 - (*α* - ethyl) - acetic acid; and
5 - (2',4' - dichlorobenzoyl) - 1 - (*n* - butyl-pyrrole) - 2 - (*α* - methyl - acetic acid.

EXAMPLE XLVIII

1 - Benzyl - 5 - (*p* - chlorobenzoyl) - pyrrole-2 - acetonitrile:

A solution of 8.43 ml. (0.0663 mole) of *p*-chlorobenzoyl chloride and 8.8 g. (0.0663 mole) of aluminum chloride in 100 ml. of 1,2-dichloroethane is added to a solution of 13.0 g. (0.0663 mole) of 1 - benzylpyrrole - 2 - acetonitrile in 50 ml. of 1,2-dichloroethane at 5°C. over a 5 minute period. The mixture is stirred for 15 minutes and then heated quickly to reflux for 3 minutes. The reaction mixture is poured into ice-hydrochloric acid and then filtered. The aqueous layer is separated and washed with chloroforrm. The combined organic solutions are washed successively with N,N-dimethylaminopropylamine solution, dilute hydrochloric acid, and brine and then dried over anhydrous magnesium sulfate. The solvent is evaporated and the oily residue dissolved in benzene-methylcyclohexane and seeded with crystals of 1 - benzyl-5 - (*p* - chlorobenzoyl) - pyrrole - 2 - acetonitrile. After crystallization of the latter substance is complete, the mother liquor is filtered and evaporated and the residue crystallized from methanol. The crystals thus obtained are recrystallized from methanol to give 1-benzyl - 5 - (*p* - chlorobenzoyl) - pyrrole - 2-acetonitrile as a yellow solid, m.p. 104—106°C.

EXAMPLE XLIX

1 - Benzyl - 5 - (*p* - chlorobenzoyl) - pyrrole-2 - acetic acid:

A suspension of 3.0 g. (0.009 mole) of 1-benzyl - 5 - (*p* - chlorobenzoyl) - pyrrole-2 - acetonitrile in 20 ml. of ethanol and 18 ml. (0.018 mole) of 1N sodium hydroxide is refluxed for 6 hours. The mixture is diluted with water and the ethanol evaporated *in vacuo*. The solution is washed with chloroform and ether and acidified with 3N hydrochloric acid. The precipitated solid is collected and dried *in vacuo* to give about 2.8 g. (91% yield) of 1 - benzyl - 5 - (*p* - chlorobenzoyl) - pyrrole - 2 - acetic acid as white crystals, M.P. 162—163°C.

Analysis: Calcd. for $C_{20}H_{15}ClNO_3$: C, 67.70; H, 4.56; N, 3.96%
Found: C, 67.79; H, 4.65; N, 3.97%

EXAMPLE L

The procedure of Example XLVIII is followed to prepare 5 - aroyl - 1 - R_1 - pyrrole-2 - acetonitrile wherein R_1 is benzyl. By repeating the procedure with an equivalent amount of an appropriate benzoyl chloride in place of the *p*-chlorobenzoyl chloride used therein, the following respective products are obtained:

1 - benzyl - 5 - benzoyl - pyrrole - 2 - acetonitrile;
1 - benzyl - 5 - (*p* - bromobenzoyl) - pyrrole-2 - acetonitrile;
1 - benzyl - 5 - (*p* - ethoxybenzoyl) - pyrrole-2 - acetonitrile;
1 - benzyl - 5 - (2',4' - dichlorobenzoyl)-pyrrole - 2 - acetonitrile; and
1 - benzyl - 5 - (3',4' - dimethylbenzoyl)-pyrrole - 2 - acetonitrile.

EXAMPLE LI

The nitrile-to-acid transformation procedure of Example XLIX is followed using an equivalent amount of each acetonitrile obtained in Example L to yield, as respective products, the corresponding 1 - benzyl - 5-aroyl - pyrrole - 2 - acetic acids.

EXAMPLE LII

The alkylation and transformation procedures of Examples XXXIV and XXXV, respectively, are repeated, except that an equivalent amount of an appropriate 1 - benzyl - 5-aroylpyrrole - 2 - acetonitrile and an equivalent amount of an appropriate alkyl halide as the alkylating agent are used to yield the following respective products:

1 - benzyl - 5 - (*p* - chlorobenzoyl) - pyrrole-2 - (*α* - methyl) - acetic acid;
1 - benzyl - 5 - benzoyl - pyrrole - 2 - [*α* - (*n*-propyl)] - acetic acid;
1 - benzyl - 5 - (*p* - bromobenzoyl) - pyrrole-2 - (*α* - ethyl) - acetic acid;
1 - benzyl - 5 - (*p* - ethoxybenzoyl) - pyrrole-2 - (*α* - methyl) - acetic acid;
1 - benzyl - 5 - (2',4' - dichlorobenzoyl)-pyrrole - 2 - (*α* - ethyl) - acetic acid; and
1 - benzyl - 5 - (3',4' - dimethylbenzoyl)-pyrrole - 2 - (*α* - methyl) - acetic acid.

EXAMPLE LIII

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole-2 - acetonitrile:

An acylating solution is prepared by the slow addition of 278 g. (1.58 moles) of *p*-chlorobenzoyl chloride to 210 g. (1.58 moles) of aluminum chloride in 750 ml. of ethylene chloride. The resulting solution is added to a solution of 190 g. (1.58 moles) of N - methylpyrrole - 2 - acetonitrile in 750 ml. of ethylene chloride. The temperautre is maintained at 20—22°C. during the addition; and the solution is further stirred at room temperature for one hour. The solution is then heated rapidly to 74—76°C. at which point there is a vigorous evolution of hydrogen chloride gas. This temperature is maintained for about 5 minutes and the solution is cooled rapidly and poured into ice water. The product is extracted with methylene chloride and washed with water. The organic solution is then shaken with an excess of an aqueous solution of N,N - dimethylaminopropylamine followed by dilute hydrochloric acid in order to remove any excess *p*-chlorobenzoyl chloride. After a final wash with brine, the solution is dried over anhydrous magnesium sulfate. Distillation of the solvent leaves a residue which crystallizes. Recrystallization from methyl alcohol yields the product, 5 - (*p* - chlorobenzoyl)-1 - methylpyrrole - 2 - acetonitrile, m.p. 120—124°C. After two additional recrystallizations from methanol, the m.p. is 127—131°C.

EXAMPLE LIV

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole-2 - acetic acid:

A mixture of 129 g. (0.52 mole) of 5 - (*p*-chlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile and 88 g. (1.1 moles) of 50% sodium hydroxide solution in 800 ml. of ethanol and 500 ml. of water is stirred and refluxed for about 18 hours with slow evolution of ammonia. The solution is then cooled to about 50°C. and acidified by adding 110 ml. of concentrated hydrochloric acid. The mixture is cooled and the precipitated product, 5 - (*p*-chlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, is filtered and recrystallized from methanol, m.p. 193—195°C. with decomposition. A second yield is obtained upon concentration of the mother liquor for a total yield of about 67% of the theoretical yield.

Analysis: Calcd. for $C_{14}H_{11}ClNO_3$: N, 5.05%
Found: N, 5.06%

EXAMPLE LV

Ethyl 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetate:

A suspension of 55.4 g. of 5 - (*p* - chlorobenzoyl) - 1 - methyl - pyrrole - 2 - acetic acid, 44 ml. of absolute ethanol, 1 g. of *p*-toluene-sulfonic acid and 650 ml. of benzene is heated under reflux with azeotropic removal of water for 7 hours. The reaction mixture is filtered, washed with sodium bicarbonate solution, dried over anhydrous magnesium sulfate and the solvent evaporated *in vacuo*. The crystalline residue is recrystallized twice from cyclohexane to give ethyl 5 - (*p* - chlorobenzoyl) - 1 - methyl - pyrrole - 2 - acetate as a yellow solid, m.p. 74—76°C.

EXAMPLE LVI

The procedure of Example LV is repeated except that an equivalent amount of isopropanol and n-butanol are used in place of the ethanol used therein to yield, as respective products, the corresponding isopropyl and *n*-butyl esters of 5 - (*p* - chlorobenzoyl) - 1-methyl - pyrrole - 2 - acetate.

PREPARATION OF INTERMEDIATE COMPOUNDS

A. Methyl 1 - methylpyrrole - 2 - acetate: Four hundred and fifty ml. of ethereal diazomethane [prepared from 43 g. (0.2 mole) of N - methyl - N - nitroso - *p* - toluenesulfonamide by the method described in Organic Synthesis, Vol. IV, John Wiley & Sons, p. 250—252, (1963) is added dropwise to a cooled solution of 18.1 g. (0.13 mole) 1-methylpyrrole - 2 - acetic acid in 100 ml. of anhydrous methanol keeping the temperature at approximately 0°C. When the evolution of gas ceases, the mixture is washed three times with saturated sodium bicarbonate solution, once with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent is evaporated, yielding about 14.5 g. of an oily residue of methyl 1 - methylpyrrole - 2 - acetate which is used without further purification in the procedure of Example XLVII.

B. Methyl pyrrole - 2 - acetate is obtained by repeating the procedure above, except that an equivalent quantity of pyrrole-2-acetic acid is used in place of the 1 - methylpyrrole - 2 - acetic acid used therein.

EXAMPLE LVII

A. Methyl 5 - (*p* - chlorobenzoyl) - 1-methylpyrrole - 2 - acetate: Ten and a half grams of *p*-chlorobenzoyl chloride is added dropwise to a chilled suspension of 8 g. (0.06 mole) of aluminum chloride in 60 ml. of methylene chloride. The resulting solution is added quickly in dropwise manner to a solution of 7.6 g. (0.05 mole) methyl 1 - methylpyrrole - 2 - acetate in 30 ml. of methylene chloride keeping the temperature below 10°C.

The reaction mixture is stirred for twenty minutes, then poured into 3N hydrochloric acid, and the resulting mixture extracted with ether. The ether fraction is washed successively with N,N - dimethyl - 1,3 - propanediamine, with 3N hydrochloric acid and with saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. The solvent is evaporated *in vacuo* and the resulting solid, methyl 5 - (*p* - chlorobenzoyl) - 1-methylpyrrole - 2 - acetate, is purified by recrystallization from methanol, m.p. 122—125°C.

B. Methyl 5 - (*p* - chlorobenzoyl) - pyrrole - 2 - acetate is obtained by repeating the procedure of Example LVII—A, except that an equivalent quantity of methyl pyrrole - 2-acetate is used in place of the methyl 1-methylpyrrole - 2 - acetate used therein.

EXAMPLE LVIII

By repeating the procedures of Example LVII (A and B), except that an equivalent quantity of an appropriate benzoyl chloride is used in place of the *p*-chlorobenzoyl chloride used therein, the following respective products are obtained:

methyl 5 - benzoyl - pyrrole - 2 - acetate;
methyl 5 - benzoyl - 1 - methylpyrrole - 2-acetate;
methyl 5 - (*p* - bromobenzoyl) - 1 - methylpyrrole - 2 - acetate;
methyl 5 - (*p* - methoxybenzoyl) - 1 - methylpyrrole - 2 - acetate; and
methyl 5 - (2',4' - dichlorobenzoyl) - pyrrole-2 - acetate.

EXAMPLE LIX

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole-2 - acetamide:

A mixture of 12.4 g. (0.05 mole) of 5-(*p* - chlorobenzoyl) - 1 - methylpyrrole - 2-acetonitrile and 8 g. of 50% sodium hydroxide solution in 50 ml. of water and 75 ml. of methyl alcohol is stirred and refluxed for 45 minutes. The resulting solid is filtered from the hot solution and recrystallized from dimethyl formamide to give about 8.5 g. (62%) of the product 5 - (*p* - chlorobenzoyl) - 1-methylpyrrole - 2 - acetamide, m.p. 250—253°C. with decomposition.

Analysis: Calcd. for $C_{14}H_{13}ClNO_2$: N, 10.13%
Found: N, 9.97%

EXAMPLE LX

The procedure of Example LIX is followed to hydrolyze the cyano function of the subject compounds to an amide function (i.e., "R_2"). By repeating said procedure with an equivalent amount of an appropriate 5-aroyl - 1 - R_1 - 2 - alkanonitrile as the starting material, the following respective products are obtained:

5 - benzoyl - 1 - methylpyrrole - 2 - acetamide;
5 - (*p* - chlorobenzoyl) - pyrrole - 2 - acetamide;
5 - (3' - chloro - *p* - toluoyl) - 1 - methylpyrrole - 2 - acetamide;
5 - (*p* - methoxybenzoyl) - pyrrole - 2-acetamide;
5 - (*p* - chlorobenzoyl) - 1 - ethylpyrrole - 2-acetamide; and
1 - benzyl - 5 - (*p* - chlorobenzoyl) - pyrrole-2 - acetamide.

EXAMPLE LXI

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole-2 - (N - ethyl) - acetamide:

A suspension of 6.0 g. (0.02 mole) of the sodium salt of 5 - (*p* - chlorobenzoyl) - 1-methylpyrrole - 2 - acetic acid in 100 ml. of dry benzene is treated with 2.1 ml. (0.025 mole) of oxalyl chloride in 100 ml. of benzene. The mixture is stirred for 3 hours, filtered, evaporated *in vacuo* and the residue taken up in benzene. The benzene mixture is poured into 50 ml. of 70% ethylamine in 200 ml. of water. The precipitated solid is filtered and dried. It is recrystallized from ethanol to give about 2.0 g. of 5 - (*p* - chlorobenzoyl) - 1-methylpyrrole - 2 - (N - ethyl) - acetamide as white needles, m.p. 187—188°C.

Analysis: Calcd. for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62; N, 9.20%
Found: C, 63.06; H, 5.61; N, 9.14%

EXAMPLE LXII

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole-2 - (N,N - diethyl) - acetamide:

To a solution of 6.1 g. (0.02 mole) of 5-(*p* - chlorobenzoyl) - 1 - methylpyrrole - 2-acetic acid in 100 ml. chloroform is added 3.8 ml. (0.03 mole) thionyl chloride. The mixture is stirred and refluxed overnight. The solvent is then evaporated and the residue is added quickly to a solution of 22 ml. diethyl-

amine in 50 ml. water while cooling externally with an ice-bath. A solid precipitates, 5-(*p* - chlorobenzoyl) - 1 - methylpyrrole - 2-(N,N - diethyl) - acetamide, which is collected and purified by recrystallization from methylcyclohexane, m.p. 82—85°C.

Analysis: Calcd. for $C_{18}H_{21}ClN_2O_2$: C, 64.96; H, 6.36; N, 8.41%
Found: C, 65.02; H, 6.38; N, 8.20%

Example LXIII

By following the respective procedures of Examples LXI and LXII, except that an equivalent amount of an appropriate 5-aroyl - pyrrole - 2 - alkanoic acid or salt thereof and an equivalent quantity of an appropriate primary or secondary alkylamine are used as starting materials, the following respective products are obtained:

5 - benzoyl - 1 - methylpyrrole - 2 - (N-ethyl) - acetamide;
5 - benzoyl - pyrrole - 2 - (N,N - diethyl)-acetamide);
1 - benzyl - 5 - (*p* - chlorobenzoyl) - pyrrole-2 - (N - isopropyl) - acetamide;
5 - (*p* - toluoyl) - 1 - methylpyrrole - 2-(N,N - dimethyl) - acetamide;
5 - (*p* - chlorobenzoyl) - 1 - ethyl - pyrrole-2 - [N - (*n* - butyl)] - acetamide; and
5 - (*p* - chlorobenzoyl) - *α* - methyl - 1-methylpyrrole - 2 - (N - ethyl) - acetamide.

Preparation of Intermediate Compounds.

The procedure described by R. Jones and J. Lindner in the Canadian Journal of Chemistry, *18*, 883 (1965), wherein N - alkylpyrrole-2 - carboxaldehydes are reacted with ethoxycarbonyl - methylene triphenylphosphorane to yield ethyl 2 - (1 - alkyl - 2 - pyrrolyl)-acrylates, is followed to prepare, as respective products, the 1-methyl, 1-(*n*-butyl) and 1-isoamyl derivatives of ethyl 2 - (2 - pyrrolyl)-acrylate.

Ethyl 2-(1-methyl-2-pyrrolyl)-propionate:

A solution of 62.4 g. (0.35 mole) of ethyl 2 - (1 - methyl - 2 - pyrrolyl) - acrylate in 350 ml. 95% ethanol is hydrogenated in a Parr shaker using 3 g. of platinum oxide as the catalyst. The hydrogenation is continued overnight under 32 p.s.i. of hydrogen. The mixture is filtered and the filtrate concentrated *in vacuo*. The residual yellow oil is dissolved in ether and washed successively with 3N hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution. The ether solution is dried over anhydrous magnesium sulfate. The ether solvent is then evaporated to yield about 42 g. of a clear oil, ethyl 2 - (1 - methyl - 2-pyrrolyl) - propionate.

Example LXIV

Ethyl 5 - (*p* - chlorobenzoyl) - 1 - methyl-pyrrole - 2 - propionate:

To a suspension of 26.6 g. (0.2 mole) of aluminum chloride in 100 ml. methylene chloride is added 34.8 g. (0.2 mole) of *p*-chlorobenzoyl chloride. The resulting suspension is added dropwise to a solution of 36.8 g. (0.2 mole) of ethyl 2 - (1 - methyl - 2-pyrrolyl) - propionate in 100 ml. methylene chloride while cooling externally with an ice bath. After the addition is complete, the reaction is stirred for 10 minutes and poured into ice acidified with dilute hydrochloric acid. The two fractions are separated. The organic fraction is washed successively with N,N - dimethyl - 1,3 - propanediamine, 3N hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution. The organic fraction is then dried over anhydrous magnesium sulfate and the solvent evaporated *in vacuo*. A solid is crystallized in the resulting oily residue which is isolated and purified by recrystallization from methanol, m.p. 71.5—73°C.

Example LXV

5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole-2 - propionic acid:

A suspension of 8.0 g. (0.025 mole) of ethyl 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole-2 - propionate in 15 ml. ethanol and 30 ml. 1N sodium hydroxide is refluxed for one hour. The ethanol is then evaporated and the remaining solution is poured into dilute hydrochloric acid. The resulting white precipitate is filtered off and purified by recrystallization from isopropyl alcohol, to give 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - propionic acid, m.p. 188—191°C.

Example LXVI

The successive procedures of Examples LXIV and LXV are repeated, except that an equivalent amount of the 1 - (*n* - butyl) and 1-isoamyl derivative of ethyl 2 - (2 - pyrrolyl)-acrylate is used initially, to yield, as respective products:

ethyl 2 - (1 - *n* - butyl - 2 - pyrrolyl)-propionate;
ethyl 2 - (1 - isoamyl - 2 - pyrrolyl) - propionate;

ethyl 5 - (*p* - chlorobenzoyl) - 1 - *n* - butylpyrrole - 2 - propionate;
ethyl 5 - (*p* - chlorobenzoyl) - 1 - isoamylpyrrole - 2 - propionate;
5 - (*p* - chlorobenzoyl) - 1 - *n* - butylpyrrole-2 - propionic acid; and
5 - (*p* - chlorobenzoyl) - 1 - isoamylpyrrole-2 - propionic acid.

EXAMPLE LXVII

A. The acylation procedure of Example LXIV is repeated, except that an equivalent amount of an appropriate ethyl 2 - (1 - alkyl-2 - pyrrolyl) - propionate and an equivalent amount of an appropriate benzoyl chloride acylating agent are employed, to yield as respective products:

ethyl 5 - (*p* - methylbenzoyl) - 1 - methylpyrrole - 2 - propionate;
ethyl 5 - (*p* - ethoxybenzoyl) - 1 - *n* - butylpyrrole - 2 - propionate;
ethyl 5 - (2',4' - dichlorobenzoyl) - 1-methylpyrrole - 2 - propionate;
ethyl 5 - (*p* - cyanobenzoyl) - 1 - isoamylpyrrole - 2 - propionate;
ethyl 5 - (*p* - methylthiobenzoyl) - 1 - methylpyrrole - 2 - propionate;
ethyl 5 - (*p* - nitrobenzoyl) - 1 - methylpyrrole-2 - propionate; and
ethyl 5 - (3',4'5' - trimethoxybenzoyl) - 1-methylpyrrole - 2 - propionate.

B. The ester-to-acid transformation procedure of Example LXV is repeated using an equivalent amount of each propionate ester obtained from Example LXVII—A in place of the ester used therein to yield, as respective products, the corresponding 5 - aroyl-1 - alkylpyrrole - 2 - propionic acids.

C. By using an equivalent amount of ethyl 5 - (*p* - nitrobenzoyl) - 1 - methylpyrrole - 2 - propionate in place of 5 - (*p*-nitrobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile in the hydrogenation procedure of Example XXIV, the product, ethyl 5 - (*p*-aminobenzoyl) - 1 - methylpyrrole - 2 - propionate is obtained.

D. By repeating the hydrolysis procedure of Example LXV with an equivalent amount of the ester obtained from Example LXVII—C in place of the ester used therein, the product, 5 - (*p* - aminobenzoyl) - 1-methylpyrrole - 2 - propionic acid is obtained.

PREPARATION OF INTERMEDIATE COMPOUNDS.

1. The procedure described by Ceresole in Ber., *17*, 815 (1884), wherein 1 - aryl - 1,3-butanediones are reacted with nitrous acid to yield the corresponding 1 - aryl - 1,2,3-butanetrione - 2 - oximes, is followed to prepare, as respective products:

1 - phenyl - 1,2,3 - butanetrione - 2 - oxime, m.p. 130—131°C.;
1 - *p* - chlorophenyl - 1,2,3 - butanetrione-2 - oxime;
1 - *p* - methylphenyl - 1,2,3 - butanetrione-2 - oxime; and
1 - *p* - methoxyphenyl - 1,2,3 - butanetrione-2 - oxime.

2A. Ethyl 5 - benzoyl - 3 - ethoxycarbonyl-4 - methylpyrrole - 2 - acetate: A solution of 71 g. (0.37 mole) of 1 - phenyl - 1,2,3-butanetrione - 2 - oxime in 350 ml. glacial acetic acid and 50 ml. of water is added to 75.5 g. diethyl acetonedicarboxylate in 350 ml. of glacial acetic acid at 70°C. Concurrently, a mixture of 73 g. (1.12 mole) of zinc dust and 91.5 g. (1.12 mole) of anhydrous sodium acetate is added in portions at such a rate that the temperature is maintained near 100°C. After the additions are complete (about 45 minutes), the mixture is refluxed for one hour and poured into iced water. The resulting crude semisolid is collected by filtration and recrystallized twice from methanol to give ethyl 5 - benzoyl - 3 - ethoxycarbonyl-4 - methylpyrrole - 2 - acetate, m.p. 152—154°C.

Analysis: Calcd. for $C_{19}H_{21}NO_6$: C, 66.46; H, 6.16; N, 4.08%
Found: C, 66.50; H, 6.20; N, 4.17%

2B. By repeating the procedure above with an equivalent amount of the 1 - *p* - chlorophenyl, 1 - *p* - methylphenyl and 1 - *p*-methoxyphenyl derivative of 1,2,3 - butanetrione - 2 - oxime, there are obtained as respective products, the corresponding ethyl 5-aroyl - 3 - ethoxycarbonyl - 4 - methylpyrrole-2 - acetates.

3A. 5 - Benzoyl - 3 - carboxy - 4 - methylpyrrole - 2 - acetic acid: A mixture of 3.4 g. of ethyl 5 - benzoyl - 3 - ethoxy - carbonyl-4 - methylpyrrole - 2 - acetate, 10 g. of 50% sodium hydroxide solution and 10 ml. of water is refluxed for 2 hours. The reaction mixture is then diluted with water and acidified with dilute hydrochloric acid. The precipitated solid is collected by filtration, air-dried, and recrystallized from acetone-water to yield the product, 5 - benzoyl - 3 - carboxy - 4 - methylpyrrole - 2 - acetic acid, as white crystals, m.p. 250—253°C.

3B. The hydrolysis procedure above is repeated, except that an equivalent amount of each ester obtained in Example LXXII—B is used, to yield, as respective products, the corresponding 5 - *p* - chlorobenzoyl, 5 - *p*-

methylbenzoyl and 5 - *p* - methoxybenzoyl derivatives of 3 - carboxy - 4 - methylpyrrole-2 - acetic acid.

4A. Ethyl 5 - benzoyl - 3 - carboxy - 4-methylpyrrole - 2 - acetate: A solution of 8.0 g. (0.028 mole) of 5 - benzoyl - 3-carboxy - 4- methylpyrrole - 2 - acetic acid in 80 ml. of 0.5% ethanolic hydrogen chloride is refluxed for 90 minutes. The solution is charcoaled, filtered, and the filtrate evaporated *in vacuo* to yield a crystalline residue which is recrystallized from acetone to give ethyl 5 - benzoyl - 3 - carboxy - 4 - methylpyrrole - 2 - acetate, m.p. 183—185°C.

4B. The partial reesterification procedure of A above is repeated using an equivalent amount of the respective acids obtained in 3B to yield the corresponding ethyl 5 - aroyl-3 - carboxyl - 4 - methylpyrrol e- 2 - acetates, respectively.

Example LXVIII

A. 5 - Benzoyl - 4 - methylpyrrole - 2-acetic acid: A solution of 4.13 g. (0.0131 mole) of ethyl 5 - benzoyl - 3 - carboxy - 4-methylpyrrole - 2 - acetate in 80 ml. of quinoline in the presence of a trace amount of copper chromite is heated at 180—183°C. for 5 hours. The mixture is poured into dilute hydrochloric acid and extracted three times with ether. The ether extracts are combined and washed successively with dilute hydrochloric acid, sodium bicarbonate solution and brine and then dried over anhydrous magnesium sulfate. The solvent is evaporated *in vacuo* to give about 4 g. of ethyl 5 - benzoyl-4 - methylpyrrole - 2 - acetate as a semisolid compound which is used in the following hydrolysis procedure without further purification.

The entire semisolid compound is dissolved in 20 ml. of ethanol and 20 ml. of 1N sodium hydroxide solution is added. The mixture is heated under reflux for 30 minutes. The solvent is then evaporated *in vacuo* and the residue dissolved in water and washed with ether. The aqueous solution is acidified with dilute hydrochloric acid and the resulting crystalline solid (1.6 g., 50% yield) is collected by filtration and air-dried. The product, 5-benzoyl - 4 - methylpyrrole - 2 - acetic acid, is recrystallized three times from acetone-water with charcoaling, m.p. 167—168°C.

B. The procedure of Example LXVIII—A is repeated using an equivalent amount of the respective esters obtained in 4B above to yield the corresponding 5 - *p* - chlorobenzoyl, 5-*p* - methylbenzoyl and 5 - *p* - methoxybenzoyl derivatives, respectively, of 4 - methylpyrrole-2 - acetic acid.

C. Lower alkyl esters of the acids obtained in A and B of this Example, such as, for example, the ethyl, isopropyl and *n*-butyl esters, are prepared by conventional esterification techniques using an appropriate lower alkanol.

D. Primary, secondary and tertiary amides of the acids obtained in A and B of this Example are prepared by conventional procedures, for example, by treatment with thionyl chloride and then contacting the thus-obtained acid chloride with ammonia, a primary lower alkylamine or a secondary lower alkylamine, compounds such as the following may be obtained:

5 - benzoyl - 4 - methylpyrrole - 2 - (N,N-diethyl) - acetamide;
5 - (*p* - chlorobenzoyl) - 4 - methylpyrrole-2 - acetamide;
5 - (*p* - methylbenzoyl) - 4 - methylpyrrole-2 - (N - methyl) - acetamide; and
5 - (*p* - methoxybenzoyl) - 4 - methylpyrrole-2 - (N - ethyl) - acetamide.

Preparation of Intermediate Compounds.

5A. Ethyl 5 - (*p* - chlorobenzoyl) - 2,4-dimethylpyrrole - 3 - acetate: To a solution of 29 g. (0.17 mole) of *p* - chlorobenzoyl chloride and 28.0 g. (0.15 mole) of ethyl 2,4-dimethylpyrrole - 3 - acetate in 100 ml. carbon disulfide, is added 41.23 g. (0.31 mole) of anhydrous aluminum chloride. The reaction mixture is cooled externally with an ice bath. The mixture is stirred for 15 minutes after which the solvent is decanted and the remaining solid treated with ice acidified with 3N hydrochloric acid. The acidic mixture is extracted three times with ether. The combined ether extracts are washed successively with N,N - dimethyl - 1,3 - propanediamine, 3N hydrochloric acid, and a saturated solution of sodium chloride. The solution is dried over anhydrous magnesium sulfate and the solvent evaporated *in vacuo*. The remaining solid is recrystallized from methanol to yield, ethyl 5 - (*p* - chlorobenzoyl) - 2,4 - dimethylpyrrole-3 - acetate, m.p. 126—129°C.

5B. By repeating the procedure of 5A above, except that an equivalent amount of an appropriate benzoyl chloride is used as the acylating agent, there are obtained as respective products:

ethyl 5 - benzoyl - 2,4 - dimethylpyrrole - 3-acetate;
ethyl 5 - (*p* - methoxybenzoyl) - 2,4 - dimethylpyrrole - 3 - acetate;
ethyl 5 - (2',4' - dichlorobenzoyl) - 2,4 - dimethylpyrrole - 3 - acetate;
ethyl 5 - (3' - chloro - 4' - methylbenzoyl)-2,4 - dimethylpyrrole - 3 - acetate.

6A. Ethyl 5 - (*p* - chlorobenzoyl) - 4-methyl - 2 - trichloromethylpyrrole - 3-acetate: To a suspension of 9.6 g. (0.03 mole) of ethyl 5 - (*p* - chlorobenzoyl) - 2,4 - dimethylpyrrole - 3 - acetate in 75 ml. ether is added dropwise 7.8 ml. sulfurylchloride, cooling externally with an ice bath. The resulting suspension is stirred at room temperature

for 15 hours. The resulting white solid, ethyl 5 - (*p* - chlorobenzoyl) - 4 - methyl - 2 - trichloromethylpyrrole - 3 - acetate, is filtered and purified by recrystallization twice from methylcyclohexane, m.p. 133—137°C.

6B. Perchlorination of the 2-methyl group in the esters obtained from 5B above is performed by repeating the procedure of 6A above.

7A. 5 - (*p* - Chlorobenzoyl) - 4 - methyl-2 - carboxypyrrole - 3 - acetic acid: A solution of 1.0 g. (0.0026 mole) of ethyl 5 - (*p*-chlorobenzoyl) - 4 - methyl - 2 - trichloromethylpyrrole - 3 - acetate in 10 ml. dioxane and 3 ml. water is refluxed for three hours. The resulting solution is cooled and extracted with chloroform. The organic fraction is extracted with a saturated solution of sodium bicarbonate. The aqueous phase is made acidic with dilute hydrochloric acid and the resulting precipitate of 5 - (*p* - chlorobenzoyl) - 4-methyl - 2 - carboxypyrrole - 3 - acetic acid is filtered and dried, m.p. 240°C.

7B. The procedure of 7A above is repeated using an equivalent amount of the 2-trichloromethyl esters obtained from 6B above to yield, as respective products, the corresponding 5 - aroyl - 4 - methyl - 2 - carboxypyrrole - 3 - acetic acids.

Example LXIX

A. 5 - (*p* - Chlorobenzoyl) - 4 - methylpyrrole - 3 - acetic acid:

A solution of 1.4 g. (0.004 mole) of 5-(*p* - chlorobenzoyl) - 4 - methyl - 2 - carboxypyrrole - 3 - acetic acid in 25 ml. quinoline is heated overnight at 160°C. under nitrogen. The reaction mixture is poured into ice acidified with hydrochloric acid. The mixture is extracted with chloroform and the organic phase is extracted with a saturated solution of sodium bicarbonate. The basic solution is made acidic with dilute hydrochloric acid and the resulting solid, 5 - (*p* - chlorobenzoyl) - 4-methylpyrrole - 3 - acetic acid, is filtered and purified by recrystallization from isopropyl alcohol, m.p. 145—147°C.

B. The decarboxylation procedure of Example LXIX—A is repeated, except that an equivalent amount of the 2 - carboxypyrrole-3 - acetic acids obtained in 7B above are used as the starting acids, to yield the corresponding 5 - aroyl - 4 - methylpyrrole - 3 - acetic acids, respectively.

C. Lower alkyl esters of the acids obtained in A and B of this Example, such as, for example, the ethyl, isopropyl and *n*-butyl esters, are prepared by conventional esterification procedures using an appropriate lower alkanol.

D. Primary, secondary and tertiary amides of the acids obtained in A and B of this Example are prepared by conventional procedures to yield the following respective amides:

5 - (*p* - chlorobenzoyl) - 4 - methylpyrrole-3 - acetamide;

5 - benzoyl - 4 - methylpyrrole - 3 - (N-ethyl) - acetamide;

5 - (*p* - methoxybenzoyl) - 4 - methylpyrrole-3 - [N - (*n* - propyl)] - acetamide;

5 - (2',4' - dichlorobenzoyl) - N,N - diethyl - 4 - methylpyrrole - 3 - (N,N-diethyl) - acetamide.

Preparation of Intermediate Compounds.

8A. 2 - Dimethylaminomethyl - 1 - benzylpyrrole: A solution of 8.2 g. (0.1 mole) dimethylamine hydrochloride in 8 ml. formalin is added dropwise to 17.12 g. (0.1 mole) of 1 - benzylpyrrole. The mixture is stirred at room temperature until homogeneity occurs (about 4 hours). The solution is poured into 10% sodium hydroxide solution and then extracted into ether three times. The combined organic fractions are washed with a saturated solution of sodium chloride, dried over magnesium sulfate and the solvent evaporated *in vacuo*. The product, 2 - dimethylaminomethyl - 1 - benzylpyrrole, is distilled at reduced pressure, b.p. 73°C., 0.025 mm. Hg.

8B. 2 - Dimethylaminomethyl - 1 - benzylpyrrole methiodide: A solution of 100 g. (0.47 mole) of 2 - dimethylaminomethyl - 1-benzylpyrrole in 200 ml. of absolute ethanol is cooled to 5°C. To this is added dropwise 29.4 ml. (0.47 mole) of methyl iodide. A white solid precipitates. The suspension is stirred until the precipitate is so thick that additional stirring becomes impossible. The solid, 2 - dimethylaminomethyl - 1 - benzylpyrrole methiodide, is filtered off and dried in vacuum.

8C. 1 - Benzylpyrrole - 2 - acetonitrile: A suspension of 88.9 g. (0.25 mole) of 2 - dimethylaminomethyl - 1 - benzylpyrrole methiodide is added to a suspension of 12.8 g. (0.26 mole) of sodium cyanide in 40 ml. dimethylsulfoxide. The mixture is heated under reflux for 3 hours and stirring at room temperature is continued overnight. The reaction mixture is poured into water and extracted three times with ether. The combined ether extracts are washed with brine and dried over anhydrous magnesium sulfate. The ether solvent is evaporated *in vacuo* to give about 41 g. of an oily residue which crystallizes upon standing. Recrystallization from methylcyclohexane yields the product, 1 - benzylpyrrole - 2 - acetonitrile, m.p. 62—63°C.

9A. 3 - Chloro - 4 - methylbenzoyl chloride is prepared by refluxing together 30 g. (0.175 mole) of 3 - chloro - 4 - methyl benzoic acid and 85 ml. thionyl chloride for about 2.5 hours, after which the excess thionyl chloride is distilled off under vacuum. The aroyl chloride product, 3 - chloro - 4 - methylbenzoyl chloride, distills over at b.p. 70—74°C., 10.25 mm. Hg.

9B. The procedure of 9A above represents a method for transforming benzoic acid derivatives to the corresponding acid chloride form. By following such procedure, except that an equivalent amount of an appropriately substituted benzoic acid is initially employed, the following aroyl chlorides are obtained:

3,4 - dimethoxybenzoyl chloride;
3 - bromo - 4 - chlorobenzoyl chloride;
2,3,5 - tribromobenzoyl chloride;
3,4 - dimethylbenzoyl chloride;
p - ethylbenzoyl chloride;
p - ethoxybenzoyl chloride; and
p - methylthiobenzoyl chloride.

EXAMPLE LXX

Primary, secondary and tertiary amides of the acids obtained in Examples LXV, LXVI, LXVII—B and LXVII—D are prepared by conventional reactions with ammonia or an appropriate alkylamine or dialkylamine to yield the following respective amides:

5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole-2 - propionamide;
5 - (*p* - chlorobenzoyl) - 1 - *n* - butylpyrrole-2 - propionamide;
5 - (*p* - chlorobenzoyl) - 1 - isoamylpyrrole-2 - propionamide;
5 - (*p* - methylbenzoyl) - 1 - methylpyrrole-2 - (N - ethyl) - propionamide;
5 - (3',4',5' - trimethoxybenzoyl) - 1 - methylpyrrole - 2 - (N,N - diethyl) - propionamide;
5 - (*p* - nitrobenzoyl) - 1 - methylpyrrole - 2-propionamide; and
5 - (*p* - aminobenzoyl) - 1 - methylpyrrole-2 - [N - (*n* - propyl)] - propionamide.

EXAMPLE LXXI

A. 1 - Benzyl - 5 - (*p* - chlorobenzoyl)-pyrrole - 2 - acetonitrile:

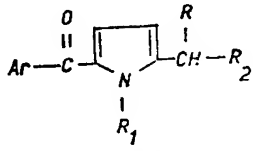
A solution of 8.43 ml. (0.067 mole) of *p*-chlorobenzoyl chloride and 8.8 g. (0.67 mole) of aluminum chloride in 100 ml. of 1,2-dichloroethane is added to a solution of 13.0 g. (0.067 mole) of 1 - benzylpyrrole - 2-acetonitrile in 50 ml. of 1,2 - dichloroethane at 5°C. over a 5 minute period. The reaction mixture is stirred for 15 minutes and then heated quickly to reflux for 3 minutes. The mixture is poured into ice-hydrochloric acid and then filtered. The aqueous layer is separated and washed with chloroform. The combined organic fractions are washed successively with N,N - dimethylaminopropylamine solution, dilute hydrochloric acid and brine and then dried over anhydrous magnesium sulfate. The solvent is evaporated to yield an oily residue from which the desired compound is isolated by column chromatography on neutral alumina with a 50—50 mixture of benzene-ether as the eluting solvent. Evaporation of the eluate affords 1 - benzyl - 5 - (*p* - chlorobenzoyl) - pyrrole - 2 - acetonitrile as a yellow solid which is recrystallized from methanol, m.p. 106—108°C.

B. 1 - Benzyl - 4 - (*p* - chlorobenzoyl)-pyrrole - 2 - acetonitrile:

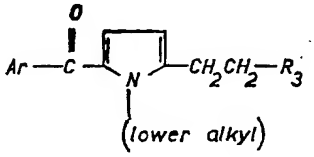
Continued elution of the column in Example LXXI—A with ethyl acetate, followed by evaporation of the eluate yields a yellow oil which crystallizes from benzene-methylcyclohexane to yield 1 - benzyl - 4 - (*p* - chlorobenzoyl) - pyrrole - 2 - acetonitrile as a white solid, m.p. 102—104°C.

WHAT WE CLAIM IS:—

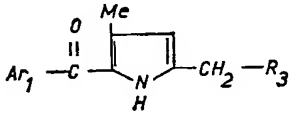
1. 5 - Aroyl - pyrrole derivatives of the general formulae:



(1—a)

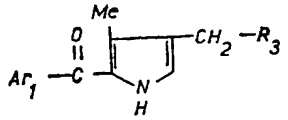


(1—b)



(1—c)

or



(1—d)

and the therapeutically acceptable basic salts of the acids thereof, wherein:

Ar represents a phenyl, monosubstituted phenyl or polysubstituted phenyl group each substituent of said substituted phenyl group being a halogen atom, a lower alkyl, lower alkoxy, nitro, amino, methylthio or cyano group;

Ar_1 represents a phenyl, monosubstituted phenyl or polysubstituted phenyl group each substituent of said substituted phenyl group being a halogen atom, a lower alkyl or lower alkoxy group;

R represents a hydrogen atom or a lower alkyl group;

R_1 represents a hydrogen atom, a lower alkyl or benzyl group;

R_2 represents a CN, COOH, COO-(lower alkyl), $CONH_2$, CONH-(lower alkyl) or CON-(lower alkyl)$_2$ group; and

R_3 represents a COOH, COO-(lower alkyl), $CONH_2$, CONH-(lower alkyl) a CON-(lower alkyl)$_2$ group;

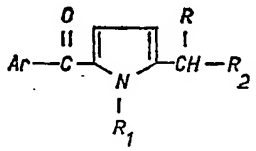
provided that:

(i) when Ar is a nitrophenyl or aminophenyl group then R is a hydrogen atom, R_1 is a lower alkyl group and R_2 is a CN, COOH or COO-(lower alkyl) group;

(ii) when Ar is a cyanophenyl or methylthiophenyl group then R_1 is a lower alkyl group and R_2 is a COOH or COO-(lower alkyl) group; and

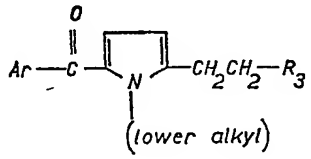
(iii) when R_1 is a hydrogen atom, then R is also a hydrogen atom.

2. 5 - Aroyl - pyrrole derivatives having the formula:



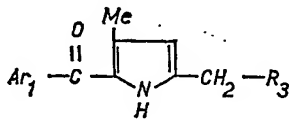
and the therapeutically acceptable basic salts of the acids thereof, wherein Ar, R, R_1, and R_2 and as defined in claim 1.

3. 5 - Aroyl - pyrrole derivatives having the formula:



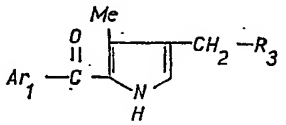
and the therapeutically acceptable basic salts of the acids thereof, wherein Ar and R_3 are as defined in claim 1.

4. 5 - Aroyl - pyrrole derivatives having the formula:



and the therapeutically acceptable basic salts of the acids thereof, wherein Ar_1 and R_3 are as defined in claim 1.

5. 5 - Aroyl - pyrrole derivatives having the formula:



and the therapeutically acceptable basic salts of the acids thereof, wherein Ar_1 and R_3 are as defined in claim 1.

6. 5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid.

7. 5 - (*m* - Chlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid.

8. 5 - (*o* - Chlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid.

9. 5 - (2^1,4^1 - dichlorobenzoyl) - 1-methylpyrrole - 2 - acetic acid.

10. 5 - (*p* - Bromobenzoyl) - 1 - methylpyrrole - 2 - acetic acid.

11. 5 - (*p* - Fluorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid.

12. 5 - (*p* - Methoxybenzoyl) - 1 - methylpyrrole - 2 - acetic acid.

13. 5 - (*p* - Methylbenzoyl) - 1 - methylpyrrole - 2 - acetic acid.

14. 5 - (*p* - Nitrobenzoyl) - 1 - methylpyrrole - 2 - acetic acid.

15. 5 - (*p* - Aminobenzoyl) - 1 - methylpyrrole - 2 - acetic acid.

16. 5 - (*p* - Cyanobenzoyl) - 1 - methylpyrrole - 2 - acetic acid.

17. 5 - Benzoyl - 1 - methylpyrrole - 2-acetic acid.

18. 5 - (*p* - Chlorobenzoyl) - α - methyl-1 - methylpyrrole - 2 - acetic acid.

19. 5 - (*p* - Chlorobenzoyl) - α - ethyl-1 - methylpyrrole - 2 - acetic acid.

20. 5 - (*p* - Chlorobenzoyl) - 1 - ethylpyrrole - 3 - acetic acid.

21. 1 - Benzyl - 5 - (*p* - chlorobenzoyl)-pyrrole - 2 - acetic acid.

22. Ethyl 5 - (*p* - chlorobenzoyl) - 1-methylpyrrole - 2 - acetate.

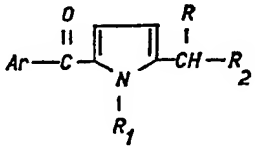
23. Methyl 5 - (*p* - chlorobenzoyl) - 1-methylpyrrole - 2 - acetate.

24. 5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole - 2 - acetamide.

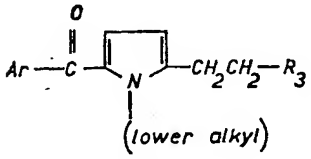
25. 5 - (*p* - Chlorobenzoyl) - pyrrole - 2-acetic acid.

26. 5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole - 2 - (N - ethyl) - acetamide.

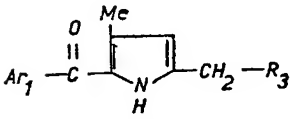
27. 5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole - 2 - (N,N - diethyl) - acetamide.
28. 5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole - 2 - propionic acid.
29. 5 - (*p* - Chlorobenzoyl - 4 - methylpyrrole - 3 - acetic acid.
30. 5 - Benzoyl - 4 - methylpyrrole - 2-acetic acid.
31. 5 - (*p* - Chlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile.
32. A process for preparing 5 - aroylpyrrole derivatives having the general formulae:



(1—a)

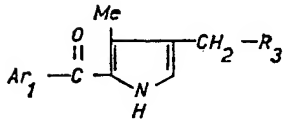


(1—b)



(1—c)

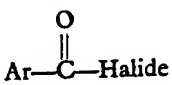
or



(1—d)

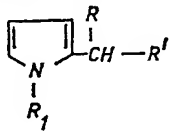
and the therapeutically acceptable basic salts of the acids thereof, wherein Ar, Ar_1, R, R_1, R_2, and R_3 are as defined in claim 1, which process comprises

(a) reacting a compound of the formula



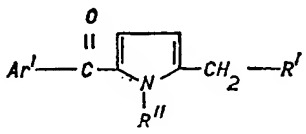
(II)

which a compound of the formula



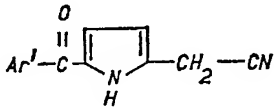
(III)

in the presence of a Lewis acid and a solvent, wherein R' is a cyano or lower alkoxycarbonyl group, whereafter, if desired, the product is converted to the corresponding free carboxylic acid by hydrolysis; or when it is desired to prepare compounds of the formula (Ia) wherein R is a lower alkyl group and R_2 is a —CN, —COO-(lower alkyl) or —COOH group, C-alkylating a compound of the formula



(V)

wherein R' is as above defined, R'' is a lower alkyl or benzyl group and Ar' is a phenyl group or a phenyl group substituted by a halogen atom, a lower alkyl, lower alkoxy or cyano group, with a lower alkyl halide in the presence of a strong base, whereafter, if desired, the product is hydrolysed to the corresponding free carboxylic acid; or when it is desired to obtain compounds wherein R_1 is a lower alkyl group, Ar is the same as Ar', R is a lower alkyl group and R_2 is a —CN or —COOH group, N-alkylating a compound of the formula

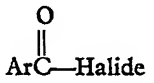


(VII)

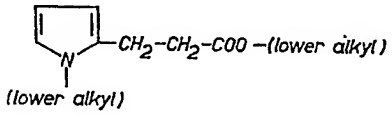
followed by C-alkylation of the product, in each case utilizing a lower alkyl halide in the presence of a strong base as the alkylating agent, and, if desired, hydrolysing the product to the corresponding acid; and in the case when Ar is a nitrophenyl group, and R_2 is the same as R', if desired, catalytically hydrogenating the nitro function to yield the corresponding compound wherein Ar is an aminophenyl group, and if desired, hydrolysing the product to the corresponding free acid form; and in the case when R_2 is a —COOH group, if desired, esterifying the said compound with a lower alkanol to yield a compound wherein R_2 is a —COO-(lower alkyl) group, and in the case when R_2 is a

—CN group, if desired, partially hydrolysing the said compound to the corresponding amide wherein R_2 is a —$CONH_2$ group; and in the case when R_2 is a —COOH group, if desired, converting the said compound to the corresponding acid chloride form followed by reacting the product with a lower alkyl-amine or a di(lower alkyl)-amine to yield the corresponding amide wherein R_2 is a —CONH (lower alkyl) or —CON (lower alkyl)$_2$ group; or

(b) reacting a compound of the formula



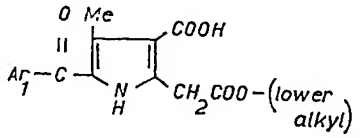
wherein Ar is as defined above and other than aminophenyl, with a compound of the formula



(IX)

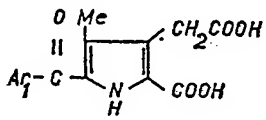
in the presence of a Lewis acid and a solvent, and, if desired, hydrolysing the resultant ester to yield the corresponding free acid of formula (1—b), and in the instance wherein Ar is a nitrophenyl group, and R_3 is a —COO-(lower alkyl) group, if desired, catalytically hydrogenating the nitro function to yield the corresponding compound wherein Ar is an aminophenyl group, and, if desired, hydrolysing the product to the free acid form; and further, if desired, converting the said acid to the corresponding amide with ammonia or an appropriate lower alkyl or di(lower alkyl)amine; or

(c) and (d) decarboxylating a compound of the formula



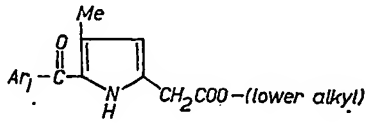
(XV)

or a compound of the formula



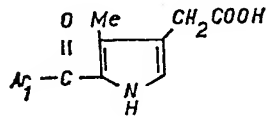
(XXII)

by heating in a basic organic solvent to prepare compounds of the respective formulae



(XVI)

and



(XXIII)

and, if desired, hydrolysing compound (XVI) to the corresponding acid, and further, if desired, esterifying compound (XXIII) with a lower alkanol or converting said acids to the corresponding amides with ammonia or an appropriate lower alkyl or di(lower alkyl) amine; and, if desired, preparing therapeutically acceptable salts of the acids of formulae (1—a), (1—b), (1—c) and (1—d) by treatment with an appropriate base.

33. A process for preparing 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises reacting ethyl N - methylpyrrole - 2 - acetate with *p* - chloro - benzoyl chloride, followed by hydrolysing the product to the free acid.

34. A process for preparing 5 - (*m* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises reacting 1 - methylpyrrole-2 - acetonitrile with *m* - chloro - benzoyl chloride, followed by hydrolysing the product to the free acid.

35. A process for preparing 5 - (*o* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises reacting 1 - methylpyrrole-2 - acetonitrile with *o* - chloro - benzoyl chloride, followed by hydrolysing the product to the free acid.

36. A process for preparing 5 - (2',4' - dichlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises hydrolysing 5 - (2',4'-dichlorobenzoyl) - 1 - methylpyrrole - 2-acetonitrile to the free acid.

37. A process for preparing 5 - (*p* - bromobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises hydrolysing 5 - (*p* - bromobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile to the free acid.

38. A process for preparing 5 - (*p* - fluorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises hydrolysing 5 - (*p* - fluorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile to the free acid.

39. A process for preparing 5 - (*p* - methoxybenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises hydrolysing methyl-(*p* - methoxy - benzoyl) - 1 - methylpyrrole - 2-acetate to the free acid.

40. A process for preparing 5 - (*p* - methylbenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises hydrolysing 5 - (*p* - methylbenzoyl) - 1 - methylpyrrole - 2 - acetonitrile to the free acid.

41. A process for preparing 5 - (*p* - nitrobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises hydrolysing ethyl - 5 - (*p*-nitrobenzoyl) - 1 - methylpyrrole - 2 - acetate to the free acid.

42. A process for preparing 5 - (*p* - aminobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises hydrolysing ethyl 5 - (*p*-aminobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile to the free acid.

43. A process for preparing 5 - (*p* - cyanobenzoyl) - 1 - methylpyrrole - 2 - acetic acid, which comprises hydrolysing ethyl 5 - (*p*-cyanobenzoyl) - 1 - methylpyrrole - 2 - acetate to the free acid.

44. A process for preparing 5 - benzoyl-1 - methylpyrrole - 2 - acetic acid, which comprises reacting 1 - methylpyrrole - 2 - acetonitrile with benzoyl chloride followed by hydrolysing the product to the free acid.

45. A process for preparing 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - (*α* - methyl)-acetic acid which comprises hydrolysing ethyl 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole-2 - (*α* - methyl) - acetate to the free acid.

46. A process for preparing 5 - (*p* - chlorobenzoyl) - *α* - ethyl - 1 - methylpyrrole - 2-(*α* - ethyl) - acetic acid, which comprises hydrolysing ethyl 5 - (*p* - chlorobenzoyl) - 1-methyl - pyrrole - 2 - (*α* - ethyl) - acetate to the free acid.

47. A process for preparing 5 - (*p* - chloro benzoyl) - 1 - ethylpyrrole - 2 - acetic acid, which comprises hydrolysing 5 - (*p* - chlorobenzoyl) - 1 - ethylpyrrole - 2 - acetonitrile to the free acid.

48. A process for preparing 1 - benzyl-5 - (*p* - chlorobenzoyl) - pyrrole - 2 - acetic acid, which comprises hydrolysing 1 - benzoyl-5 - (*p* - chlorobenzoyl) - pyrrole - 2 - acetonitrile to the free acid.

49. A process for preparing ethyl 5 - (*p*-chlorobenzoyl) - 1 - methylpyrrole - 2-acetate, which comprises reacting ethyl N-methylpyrrole - 2 - acetate with *p* - chlorobenzoyl chloride.

50. A process for preparing methyl 5 - (*p*-chlorobenzoyl) - 1 - methylpyrrole - 2-acetate, which comprises reacting methyl 1-methyl - pyrrole - 2 - acetate with *p* - chlorobenzoyl chloride.

51. A process for preparing 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetamide, which comprises partially hydrolysing 5 - (*p*-chlorobenzoyl) - 1 - methyl - pyrrole - 2-acetonitrile to the corresponding amide.

52. A process for preparing 5 - (*p* - chlorobenzoyl) - pyrrole - 2 - acetic acid, which comprises hydrolysing 5 - (*p* - chlorobenzoyl)-pyrrole - 2 - acetonitrile to the free acid.

53. A process for preparing 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - (N - ethyl)-acetamide, which comprises reacting 5 - (*p*-chlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid with oxalyl chloride, followed by reacting the products with ethylamine.

54. A process for preparing 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetamide, (N,N - diethyl) - acetamide, which comprises reacting 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetic acid with thionyl chloride, followed by reacting the product with diethyl-amine.

55. A process for preparing 5 - (*p*-chlorobenzoyl - 1 - methylpyrrole-2-propionic acid, which comprises hydrolysing ethyl 5-(*p* - chlorobenzoyl) - 1 - methylpyrrole - 2-propionate to the free acid.

56. A process for preparing 5 - (*p* - chlorobenzoyl) - 4 - methylpyrrole - 3 - acetic acid, which comprises decarboxylating 5 - (*p*-chlorobenzoyl) - 4 - methyl - 2 - carboxypyrrole - 3 - acetic acid by heating in quinoline.

57. A process for preparing 5 - benzoyl-4 - methylpyrrole - 2 - acetic acid, which comprises hydrolysing ethyl 5 - benzoyl - 4-methylpyrrole - 2 - acetate to the free acid.

58. A process for preparing 5 - (*p* - chlorobenzoyl) - 1 - methylpyrrole - 2 - acetonitrile, which comprises reacting 1 - methylpyrrole-2 - acetonitrile with *p* - chloro - benzoyl chloride.

59. A process for preparing compounds (I—a), (I—b), (I—c) or (I—d) as claimed in claim 1, substantially as hereinbefore described with reference to any one of the accompanying examples.

60. A compound as claimed in claim 1 whenever prepared by the process as claimed in any one of claims 32 to 59.

61. An anti-inflammatory agent comprising a compound as claimed in any one of claims 1 to 31, and a pharmaceutically acceptable carrier therefor.

BOULT, WADE & TENNANT,
111 & 112, Hatton Garden, London, E.C.1.
Chartered Patent Agents,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.